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Triclofos - Promethazine and a Combination of Triclofos Promethazine and Melatonin for Sedation during MRI in Children

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Abstract

Introduction: The objective of the present study was to compare efficacy in sufficient sedation between two groups (triclofos - promethazine and a combination of triclofos promethazine and melatonin)

Method: In a randomized clinical trial, 6 months to 6 year-old children who underwent MRI, were randomly assigned where group1 received Triclofos 75mg/kg and Promethazine 0.5mg/kg ([T+P]) and 2nd group Group [T+P+M] will receive Triclofos 75mg/kg , Promethazine 0.5mg/kg and Melatonin 1 tab (3mg) in 6months-2 years, 2 tab(6mg) in >2-5 years and 3tab(9 mg) in >5 years . The primary outcomes were effective sedation and successful completion of MRI scan. Secondary outcomes were onset and duration of sedation, total stay time in the MRI unit and adverse events.

Result and Conclusion: We conclude that there was no statistically significant difference in the number of sufficient sedation and number of successful MRIs between the two groups but it was observed that the T+P+M group had better efficacy attaining sufficient sedation than the T+P group. To support this study more research is required.

Keywords: Melatonin, MRI, Pediatric Sedation, Procedure sedation

Introduction

Magnetic resonance imaging (MRI) is a noninvasive, radiation free diagnostic test that uses a magnetic field and radio waves to produce detailed images of the body's organs and structures. MRI has become the diagnostic modality of choice due to its excellent image resolution for conditions of the brain, spinal cord, muscles and abdomen. The frequency of MRI scans in children has increased in recent years owing to

significant improvements in MRI opening up new diagnostic perspectives. For optimum MRI image quality enabling precise diagnosis, patients have to remain motionless. If young patients are unable to cooperate, especially those with mental retardation and developmental delay, sedation is required. Further, the MRI takes a long time and is often quite noisy and claustrophobic. This not only makes it difficult to perform a good study in children but also poses a challenge to achieving safe and effective sedation.[1]

Goals of sedation in the pediatric patient for diagnostic and therapeutic procedures are:

1. Guard the patient's safety and welfare
2. Minimize physical discomfort and pain
3. Control anxiety, minimize psycho- logical trauma
4. Maximize the potential for amnesia
5. Control behavior and/or movement to allow the safe completion of the procedure
6. Return the patient to a state for safe discharge from medical supervision.[1]

Sedation is less invasive, cost and time saving, but the rate of failure and incidence of complications vary widely from one study to another.[2] Sedation keeps the child still for the duration of image acquisition, although there is no consensus in the pediatric community as to which pharmacological agent is best in this setting. Sedation is given mainly by routes: i.v. and oral. Adverse event rates are evenly distributed across the different sedative agents and routes.

Adverse events are usually minor including prolonged sedation and at times vomiting. Sometimes airway compromise can also occur due to difficulties owing to a reduced conscious level. Severe adverse events, such as severe respiratory depression and death, are rare.

There are many i.v. sedative agents available for pediatric imaging including etomidate, propofol, dexmedetomidine and midazolam. Oral agents used for sedation in imaging include chloral hydrate, promethazine, hydroxyzine, alimemazine (trimeprazine) and melatonin. The success rates of these different agents have been reported as between 50% and 100%.[3]

In our hospital approximately 700 scans are being performed on pediatric patients each year. Most of these scans need sedation in order to keep the patient still and acquire a clear image. Sedation under General Anesthesia or i.v. sedation can be resource intensive. So we sought to devise an oral sedation regimen that could be used safely and effectively for pediatric imaging, given the above restrictions.

Our aim of research was to compare the efficacy and safety between combination of triclofos plus promethazine and combination of triclofos plus promethazine plus melatonin in pediatric MRI sedation.

Aims and Objectives

Aim: To compare efficacy in sufficient sedation between two groups.

Objectives

1. To compare the onset of sedation and duration of sedation among two different groups.
2. To compare total no of successful MRI scan, total stay time in MRI center, adverse effects between two groups.

Material and Method

Study Area: Department of Paediatrics and Radiodiagnosis, at Santokba Durlabhji Memorial Hospital (SDMH), Jaipur

Study population: The present study was conducted on 100 pediatric patient of age group 6months - 6 yrs undergoing MRI. Patients were randomly divided into two groups who received Triclofos and Promethazine

[T+P] Or Triclofos, Promethazine and Melatonin[T+P+M].

Study type: Randomized comparative study.

Inclusion criteria

1. Patient in age group 6 months-6years.
2. Having ASA [American Society of Anesthesiology] grade 1 and 2
3. Patients whose attendant gave written informed consent to be included in study.
4. Patient scheduled for MRI.

Exclusion criteria

1. Age < 6 months and >6yrs.
2. Having ASA (American Society of Anesthesiology) grade 3 & 4.
3. Patients in whom written informed consent could not be taken.
4. Critically ill patient.
5. Patient with known allergy to above drugs.

Study design: Prospective interventional study.

Study duration: September 2017 to Dec 2018.

Outcome measure

Primary: Effective sedation, successful completion of MRI Scan.

Secondary: Onset and duration of sedation, total stay time in MRI unit, adverse event.

Method

Allocation of groups: The patients were allocated either of the two groups by randomization. The two study groups were:

1. Group [T+P] will receive Triclofos 75mg/kg and Promethazine 0.5mg/kg.
2. Group [T+P+M] will receive Triclofos 75mg/kg , Promethazine 0.5mg/kg and Melatonin 1 tab (3mg) in 6months-2 years, 2 tab(6mg) in >2-5 years and 3tab(9 mg) in >5 years.

Patients were randomized by computer generated random numbers to receive either of the above regime mentioned. Sedation level was observed every 20 minutes. After the child was adequately sedated (Ramsay sedation score >4, he/she was taken for MRI. If the patients in either of the group did not achieve the desired score of 5-6 after 60 minutes of given drug, an additional dose of Triclofos and Promethazine in the range of 35-75mg/kg and 0.25-0.5mg/kg respectively was given. Again the patient was observed for adequate sedation.

Sedation was considered a failure if the procedure had to be aborted due to the child's inability to cooperate or remain immobile despite supplemental sedation. Vitals were monitored during the procedure. The following data were recorded: sedative agents used and its dosage, their time of administration, sedation scores, the procedure start and end times, the child's discharge time, and all adverse events including hypoxemia, nausea, vomiting, sedation failure and paradoxical reactions. Parents were told to observe events that occurred following discharge, and were contacted by telephone 24 h after discharge to review the information. The following information was obtained: adverse events due to sedative medications including nausea, vomiting, diarrhoea, irritability, sleepiness, motor incoordination and the time that the child returned to baseline activity.

Observation and Results

A. Onset, duration of sedation and total stay time in MRI unit

In the T+P+M group, out of total (n=50) patients 49 (98%) were sedated after supplemental dose. Whereas in the T+P group, out of total (n=50) patients 47(94%) were sedated after supplemental dose. So the mean of induction time, duration of

sedation and total stay time in the MRI unit was taken out of 49 and 47 patients in T+P+M and T+P group respectively.

Table 1: Comparison of Mean of Sedation Parameter Variables between the Two Groups

	Group	N	Mean	SD	Median	Min.	Max.	'p' value*
Induction time (Min)	T+P+M	49	48.96	30.62	38	10	135	0.829
	T+P	47	47.62	29.89	35	6	140	
Duration of Sedation (min)	T+P+M	49	208.67	43.29	210	150	330	<0.001
	T+P	47	167.66	54.98	150	90	330	
Total stay time in MRI unit (Min)	T+P+M	49	78.14	32.35	68	30	165	0.803
	T+P	47	76.53	30.51	65	26	155	

There was no significant difference between the induction time and mean total stay time in the MRI unit of the two groups. But, there was a significant difference in the duration of sedation between the two groups. It signifies longer duration of sedation in T+P+M group compared to T+P group which attributes to use of an extra medicine in the form of melatonin in T+P+M group.

B. Comparison of adequate Sedation in between both the groups

Table 2: Comparison of Adequate sedation in between both groups

Sedated	Group [T+P+M]		Group [T+P]		Total	
	No.	%	No.	%	No.	%
Adequate	41	82.00	38	76.00	79	79.00
Inadequate	8	16.00	9	18.00	17	17.00
Failed	1	2.00	3	6.00	4	4.00
Total	50	100.00	50	100.00	100	100.00

p value-0.556

Though no of failed and inadequate sedation were more in the T+P group compared to T+P+M group, there is no statistically significant difference in no adequate sedation between both groups. This result may contribute to the sample size.

It was observed (Table 3) that there is no significant statistical difference in no inadequate sedation (requiring extra dose) with respect to age in the T+P+M group. It signifies that T+P+M combination is more efficacious than T+P group in attaining sufficient sedation in patients of older age groups.

Table 3: Relation of age with frequency of inadequate sedation in T+P+M group.

	Sedated			Total
Age(years)	Yes	inadequate	No/Failed	
<2	6	2	0	8
2-4	27	3	0	30
4-6	8	3	1	12
Total	41	8	1	50

p value- 0.241

As shown in Table no 4 that there was no significant difference in no of adequate sedation in between both groups and in no of inadequate sedation in T+P+M group (table 3), but it was observed that in T+P group there is significant difference in no of inadequate sedation (requiring extra dose) with respect to age (Table 4). It signifies that the T+P regime is more efficacious in attaining sufficient sedation in the age group younger than 2 compared to the older age group.

Table 4: Relation of age with frequency of inadequate sedation in T+P group

Age(years)	Sedated			Total
	Yes	inadequate	No/Failed	
<2	14	0	0	14
2-4	20	7	1	28
4-6	4	2	2	8
Total	38	9	3	50

p value-0.024

C. Total no of Successful MRI Scan

No statistically significant difference was seen in the number of successful MRI.

Table 5: Comparison of success in completing MRI examination in both groups

Procedure	Group [T+P+M]		Group [T+P]		Total	
	No.	%	No.	%	No.	%
Unsuccessful	1	2.00	3	0.00	4	4.00
Successful	49	98.00	47	94.00	96	96.00
Total	50	100.00	50	100.00	100	100.00

p value- 0.617

D. Adverse Effects

In our study (Table 6), 4.08% (N=2) patients had excessive sleepiness in the T+P+M group and 2.13% (N=1) patients in the T+P group. There is no statistically significant difference between the two groups.

Table 6: Comparison of sleepiness between both the groups

Sleepy	Group [T+P+M]		Group [T+P]		Total	
	No.	%	No.	%	No.	%
No	47	95.92	46	97.87	93	96.88
Yes	2	4.08	1	2.13	3	3.12
Total	49	100.00	47	100.00	96	100.00

p value- 1.000

In our study (Table 7) there is no statistically significant difference between the two groups.

Table 7: Comparison of irritability between both the groups

Irritable	Group [T+P+M]		Group [T+P]		Total	
	No.	%	No.	%	No.	%
No	46	93.88	45	95.74	91	94.79
Yes	3	6.12	2	4.26	5	5.21
Total	49	100.00	47	100.00	96	100.00

p value-1.000

In our study (Table 8), there is no statistically significant difference between the two groups,

Table 8: Comparison of vomiting between two groups

Vomiting	Group [T+P+M]		Group [T+P]		Total	
	No.	%	No.	%	No.	%
No	48	97.96	44	93.62	92	95.83
Yes	1	2.04	3	6.38	4	4.17
Total	49	100.00	47	100.00	96	100.00

p value- 0.3

Discussion

Computerized tomography (CT) and Magnetic Resonance Imaging (MRI) are two of the most common procedures requiring sedation in children. It is widely accepted that effective sedation is part and parcel of a successful MRI scanning service and an organized pediatric sedation program that is safe and effective has been recommended for all the centers offering these services, but this is far from being realized.

A. Induction Time and Duration of sedation

Mean induction time in the T+P group is 47.62 ± 29.89 minutes and in the T+P+M group is 48.96±30.62, with no statistically significant difference. In our study, more than 50% patients attained sufficient sedation within 45 min of drug intake in both the groups, but 5 patients in T+P+M

group and 3 patients in T+P group who didn't require supplemental dose took more than 60 minutes to attain sufficient sedation.

The results of randomized control trial by **Fallah et al[4]** showed that combination of chloral hydrate at minimum dosage and hydroxyzine or midazolam were equally effective in children who underwent MRI and efficacy of both the combination of the drug in sedation induction were not statistically different in infants (less than two years old) and children.

It was observed in this study that the mean duration of sedation in T+P group is 167±54.98 minutes and in T+P+M group is 208±43.29 minutes which was statistically significant (p value-0.01) Most likely reason would be addition of addition of an extra drug melatonin to the T+P+M group.

We do not have available literature with these specific combinations being evaluated, so as to compare with the results of our study. But here are studies comparing multiple oral sedatives medications for procedures like EEG and also some for neuroimaging.

Dirani et al[5] conducted a study which included a total of 803 children, 418 children underwent an EEG following the implementation of the new sedation policy, which consists of the sequential administration of melatonin, hydroxyzine (if needed), and CH (if needed). The comparator group included children (n=385) with a recorded EEG when the sedation policy consisted of the sole administration of CH. Children with a mean age of 7.9 years were included. Time to sleep onset and duration of sedation were not significantly different between the 2 policies. The study done by **Fallah et al[6]** showed that in groups of chloral hydrate and antihistamine combination (hydroxyzine or promethazine), as compared to sole chloral hydrate group, total stay time in EEG unit was shorter and the parents were more satisfied by waiting less in the EEG unit.

B. Total stay time in MRI

Mean total stay time in the MRI unit in the T+P group is 76.53±30.51 minutes and in the T+P+M group is 79.15±33.06 minutes, with no significant difference between both groups. This signifies that it took an equal amount of time for completion of the MRI and parents waited for equal amount of time in the MRI unit in both the groups.

Results in studies done by **Fallah et al[4,6]** for EEG are in fact different from our study results. **Fallah et al[4]** conducted a study in which children were randomly assigned to two groups to receive either 40 mg/kg of chloral hydrate and 2 mg/kg of hydroxyzine (Group I) or 40 mg/kg of chloral hydrate and 0.5 mg/kg of midazolam (Group II). Study showed that EEG recording in the chloral hydrate and hydroxyzine group was completed in less time compared to the chloral hydrate and midazolam group. Similar results were seen in study by **Fallah et al[6]** in which the total stay time in the MRI unit in chloral hydrate and antihistamine (hydroxyzine or promethazine) group was less compared to sole chloral hydrate group.

C. Adequate Sedation and Successful MRI

In our study, adequate sedation (Ramsay Sedation score of more than four) obtained after supplemental dose of sedative drugs in T+P group and in T+P+M group is 94% and 98% respectively. There is no statistically significant difference in the number of adequate sedation between both groups. This result may contribute to the small sample size. **Fallah et al[6]** conducted study which showed adequate deep sedation and completion of MRI examination in 23 (76.7%) children in chloral hydrate- hydroxyzine group and in 22 (73.7%) children in chloral hydrate-

midazolam group, and the statistical analysis showed that the efficacy of both drugs combination in the sedation induction was not statistically different (p=0.76). He also concluded that efficacy of both drugs combined in sedation induction was not statistically different in children with and without developmental delay, in infants (less than two years old), and also in children.

Similar results were observed in our study in terms of developmental status but as for age there was a statistically significant difference in inadequate sedation in T+P group . Hence in our study we found that T+P+M is a better drug combination for the older age group.

But other studies have shown different results for various age groups. **Vade et al**[7] conducted a study which showed 3% frequency of failed sedation in children less than 1 year age who received only chloral hydrate and underwent MRI. Patients in 1-4 age group received chloral hydrate and hydroxyzine. Logically, one would expect higher failure rate in age group 1-4 years. However, he did not encounter failures in this age group. Chloral hydrate and hydroxyzine provided better sedation compared to high dose chloral hydrate only.

Fallah et al[8] stated that adequate sedation was obtained in 43% of Promethazine (PZ) and 100% in Chloral hydrate(CH) group. EEG after adequate sedation was recorded in 70% of PZ and 96.7% of CH group. So, CH is more effective than promethazine.

D. Adverse effects

In our study, common adverse effects noted post sedation were vomiting, ataxia, excessive sleepiness and irritability which was similar to the study conducted by **Malviya et al**[9] who found a high incidence of motor imbalance, agitation, gastrointestinal effects, and restlessness after discharge. They also observed that chloral hydrate was more commonly associated with imbalance compared with midazolam, and restlessness and prolonged imbalance were associated with younger age. In our study, both sedation regimens were safe and no serious clinical adverse events were seen in the two groups.

Lee et al[10] study with the total of 1590 patients, 104 subjects reported vomiting/spitting (6.5%), which was the most common adverse effect, with 31 patients showing hyperactivity (1.9%). There were no cases of cardiorespiratory depression. But, in **Fávero et al**[11] study, two of 41 children who received chloral hydrate in dosage of 50 mg/kg had respiratory depression and in **Heistein et al**[12] study, severe adverse events such as apnea happened in 0.3 %, airway obstruction in 1.4 %, hypoxia in 5.9 %, hypercarbia in 6.6 % and hypotension in 0.4 % of kids who received chloral hydrate for echocardiography sedation. Since no significant adverse effects were noted in both the drug combination considered in our study, it is safe to use the above drug combination (T+P+M & T+P) as sedatives in non-invasive procedures and it also decreases the need for IV sedation and general anesthesia.

Limitations of our study are that our study had a relatively smaller sample size. Larger number of cases are needed for the study to reach a definitive result and conclusion. The confounding factors will be overcome by a large number of cases. Our data are only the result of a single center study and it may not be possible to generalize our result. Further studies include in the multicenter randomized trial with more patients are needed to generalize our results.

Conclusion

From our study titled "A comparative between triclofos - promethazine and a combination of triclofos - promethazine and melatonin for sedation during Magnetic Resonance Imaging [MRI] in children" it can be concluded that: There was no statistically significant difference in number of sufficient sedation and number of successful MRI between the two groups but it was observed that T+P+M group had better efficacy attaining sufficient sedation than T+P group. To support this study more research is required.

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