Comparison of Oral Trichlophos and Intranasal Midazolam for Sedation in Minimally Invasive Paediatric Procedures (RAMT Study)

Sharma M[1], Kamal K Yenamandra[2], Kalita J[3], Dash S[4], Singh D[5]

Abstract

Introduction: Uncooperative child does not allow completion of procedures, denying valuable data required for clinicians. **Material and Methods:** An open labelled parallel group prospective randomized control study was conducted at zonal hospital Jorhat. We evaluated 200 children randomized into two groups using computer based randomization. Participants aged 3 months to 5 years (*n*=200) were randomized to receive 50 mg/kg Triclofos sodium orally or intranasal spray of midazolam 0.2 mg/kg. **Results:** Adequate sedation (Ramsay reactivity score of 3 and 4) was obtained in 86% children in midazolam group as compared to 80% in triclofos group with p value of 0.138. Mean duration for onset of sedation was 20 min +/- 5.4 min in Trichlophos group and 12 min +/- 4.5 min with Intranasal Midazolam which was statistically significant with *p*-value of <0.001. The mean duration of post procedural sedation was found to be 24.00±9.21 min in midazolam group and 49.00 ± 16.99 min in triclofos group (*p*=<0.001) which was statistically significant. No significant difference was seen for side effects frequency between the two drugs (15% in Triclofos, 10% in Midazolam group; *p*=0.285). **Conclusion:** We conclude that intranasal midazolam is more effective than oral trichlophos with a comparable safety profile.

CTRI Trial Number: /2017/08/009448.

Key words: Trichlophos, Midazolam, Sedation, Ramsay score

Introduction

Paediatric procedural sedation has evolved rapidly over the last two decades because of the increased awareness about the presence of procedure-related anxiety and pain even in the youngest children. The management of acute pain and anxiety in children undergoing therapeutic and diagnostic procedures outside the operating room has developed substantially in the past 15 years[1-2]. Midazolam in current times has emerged as an ideal drug for procedural sedation having all the desirable properties in this regard. Midazolam has been used by several routes like IV, IM, rectal and Intranasal for sedation. Intravenous Midazolam is the fastest mode of sedation but rarely associated with serious side effects like hypotension, hypoxia and cyanosis, severe vomiting, intractable irritability and agitation, apnoea, laryngospasm

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Acknowledgements: None
Funding: Nil
Conflict of Interest: None
Permission from IRB: Yes

How to cite
Sharma M, Kamal K Yenamandra, Kalita J, Dash S, Singh D. Comparison of Oral Trichlophos and Intranasal Midazolam for Sedation in Minimally Invasive Paediatric Procedures (RAMT Study). J Nepal Paediatr Soc 2018;38(2):80-83.

doi: http://dx.doi.org/10.3126/jnps.v38i2.19139

and bradycardia and hence should be administered in intensive care settings. Intranasal midazolam produces high and fast concentrations in CSF with probably lesser adverse effects[3]. Monosodium trichloroethyl phosphate (trichlorofos) or Triclofos sodium is the phosphate ester of trichloroethanol, the pharmacologically active metabolite of chloral hydrate[4]. Chloral hydrate is one of the sedatives most commonly used. It has excellent absorption, fast induction and minimal effects on respiration but is limited by unpleasant taste and gastric irritation[5]. It results in less gastric irritation and has a less unpleasant taste than chloral hydrate, and it is, therefore, more acceptable for oral administration in children. A hypnotic potency equal to chloral hydrate has been reported[6].Triclofos for procedural sedation in children has been used extensively[7]. It is administered at a dose of 50-100 mg/k body wt to a maximum dose of 2 gm. Main advantages are ease of administration and least side effects and anaesthesia related complications[8].

Materials and Methods

An open labelled parallel group prospective randomized control study was conducted at zonal hospital Jorhat. Study was conducted over 03 months from Aug 17 to Oct 17.We evaluated 200 children randomized into two groups using computer based randomization. Participants aged 3 months to 5 years (*n*=200) were randomized to receive 50 mg/kg Triclofos sodium orally or intranasal midazolam 0.2 mg/kg. Ethical clearance was taken from ethical committee of the hospital. Trial was registered in CTRI reference number CTRI/2017/08/009448 after clearance from Ethical and Scientific committee clearance from the hospital. Written informed consent from parents was taken for all children enrolled in the study.

A sample size of 200 children was needed (100 children in each group) to detect a 20% difference in efficacy between the two drugs with type one error (alpha) of 0.05 and 80% power. Eligible participants included children aged three months to five years, scheduled for diagnostic procedures. Exclusion criteria consisted of presence of rhinosinusitis, neuropsychiatric illness or any other serious systemic disease, severe systemic reaction, and receiving a sedative hypnotic agent within the past 48 hours. The trial used computer generated randomization and allocation ratio was 1:1 for the two groups. Randomisation was done by an investigator with no clinical involvement in the trial. The primary outcomes were efficacy in adequate sedation and completion of procedure. Secondary outcomes included clinical side effects, serious adverse events (hypotension, hypoxia and cyanosis, severe vomiting, intractable irritability and agitation, apnoea, laryngospasm and bradycardia), and duration of post-procedural sedation. Respiratory depression requiring assisted ventilation, oxygen saturation of less than 90%, or a 25% or greater decrease in pre sedation mean arterial blood pressure were considered as serious side effects. Failure to achieve adequate sedation (patient awakened or moved, interfered with completion of procedure, inadequate sedation and need for administration of other sedative drug) and procedure abortion due to serious adverse events, were considered as failure of sedation regimen. The children were randomized to receive either single dose of 50 mg/kg oral Triclofos (Group A) or 0.2 mg/kg intranasal midazolam (Group B). Modified Ramsay sedation scale and reactivity score was used for assessment of sedation level[9]. If the child did not achieve a sedation score of 1 or reactivity score of 3 within 20 minutes of receiving the drug and did not allow the procedure to be completed, or the child had an adverse event which precludes conduct of the procedure, or the child required another drug to be administered for smooth conduct of the procedure were considered as sedation failure. All the statistical analysis was performed using SPSS version 20. The clinical profile of patients was analysed by chi-square test for qualitative variables. Student t test was performed for comparison of quantitative variables. Probability level of 5% was considered as statistically significant i.e., $p<0.05$.

Results

A total of 200 children were randomized into two groups; Group A received oral Triclofos and group B received intranasal midazolam. There was no significant difference between two groups in age, and sex (Figure 1).

The sex distribution in midazolam group was: 47 Male and 53 female children as compared to triclofos group which had 60 Male & 40 female children. The difference was not statistically significant (p value=0.065)

We compared two drugs for procedural sedation during following procedures as shown in fig 2.

Two drugs were compared in 07 different procedures. The difference of number various procedures in two study groups was not statistically significant (p-value < 0.05).

In the present study, all children were assessed for procedural sedation till 25 minutes. The best sedation score out of the two sets were taken for comparison. It was observed that in midazolam group, 86 children out of 100 had satisfactory level of sedation (sedation level 2, 3, 4) and rest of 14 children were agitated.

In Triclofos group 80 children had satisfactory level of sedation (2,3,4) and the remaining 20 were agitated. Difference between both the groups was not statistically significant with *p*-value of 0.138 (Table:1).

Mean duration for onset of sedation was around 20 min +/- 5.4min in Trichlophos group in comparison with Intranasal Midazolam which was 12 min +/- 4.5min which was statistically significant with a p- value of <0.001.

Both the drugs were compared for "ease of procedure completion" meaning need of additional doses of particular drug required to complete the procedure. In triclofos group 30% children required the use of additional dose and in Midazolam group 22% additional dose was required to complete the procedure. The difference was not statistically significant with P value of 0.197 (Table: 2)

Vital parameters like Heart rate, respiratory rate, NIBP, SpO_2 were monitored during procedural sedation. There were no significant changes in vital parameters in both the study groups. There was a decrease in respiratory rate from 30 to 26 per min in the intranasal midazolam group over a 15 min period. This decrease is within the normal range observed in children of this age group.

The mean duration of post procedural sedation was found to be 24.00±9.21 min in midazolam group and 49.00 ± 16.99 min in triclofos group (p =<0.001) which was statistically significant. The median score with respect to duration of post procedural sedation (time in minutes) found to be higher in triclofos group compared to Midazolam (49 min. vs.24 min) and this difference is highly significant. Therefore, we observed that, children in intranasal midazolam group regained consciousness in lesser time than those in oral triclofos.

Post procedural following parameters were assessed at 10 min interval for a period of 30 min, for colour, maintenance of airway, level of consciousness, movement of all four limbs and vital parameters like Respiration, HR, NIBP, SpO_2. Children were considered fit if above parameters were found within normal range as per age and sex.

Adverse events were monitored during and after completion of study. No child in either group experienced laryngospasm or emergence phenomena. Only adverse event noted was vomiting. 15 children in triclofos group experienced vomiting as compared to 10 in midazolam group. The difference was not statistically significant with *p*-value 0.285

Discussion

In our study, midazolam group did better in terms of better reactivity score and less post procedural sedation for children undergoing various procedures in comparison with oral trichlophos. Bhatnagar[4] et al, found that the oral midazolam produced better sedation than the oral triclofos. They compared oral midazolam

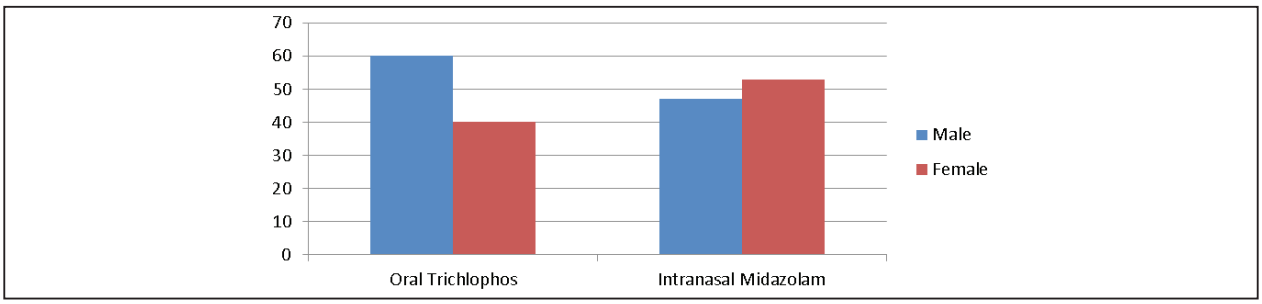

Fig 1: Showing demographic distribution of patients

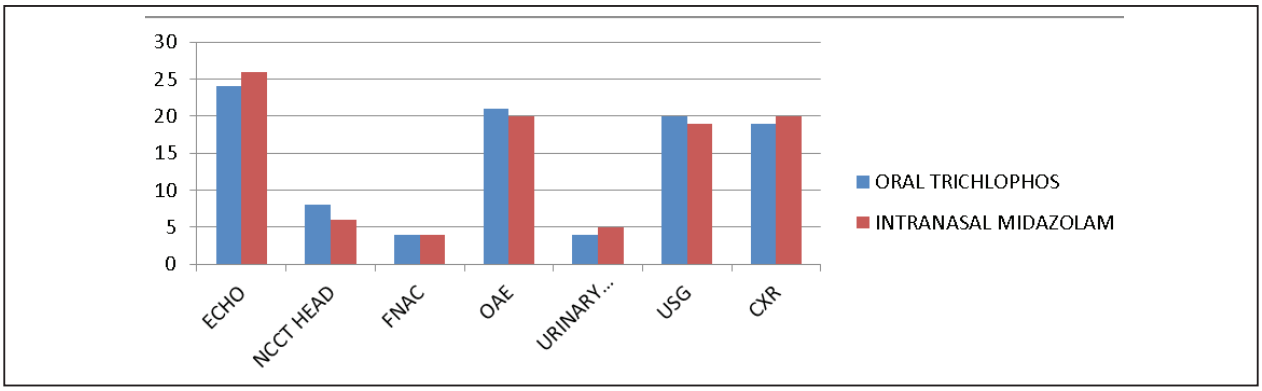

Fig 2: Showing procedures done in both groups

Table 1: Sedation score of patients in the two groups

Drug	Sedation Score				Total	*p*-value
	1	2	3	4		
Oral Triclofos	20	40	33	7	100	0.138
Intranasal Midazolam	14	56	23	7	100	
Total	**34**	**96**	**56**	**14**	**200**	

Table 2: Ease of completion of procedure in two groups

Drug	Procedure Completed		Total	P-Value
	Yes	Yes With Additional Dose		
Oral Triclofos	70	30	100	0.197
Intranasal Midazolam	78	22	100	
Total	**148**	**52**	**200**	

with oral tramadol, triclofos and zolpidem in the sedation of paediatric dental patients. Our results are in agreement with another study by Singh[9]et al, who used triclofos (70 mg/kg) as a sedative agent and concluded that midazolam oral (0.5mg/kg) gave better results as compared to triclofos in producing sedation. we used lower dose of 0.2mg/kg of intranasal midazolam and similar results were also obtained by Manjushree Roy[10] et al, who compared two doses of intranasal midazolam with that of NS and concluded that majority of the children in midazolam group had significant level of sedation at 10 min with 0.2 mg/kg. There was no added advantage of giving higher dose. Our results are not consistent with Fallah[6] et al, who conducted a single blind randomized clinical trial to compare the efficacy and safety of oral chloral hydrate in dose of 100mg/kg and intranasal midazolam 0.2mg/kg for induction of sedation for computerized tomography scan of brain in children. Lower efficacy of oral triclofos in sedation induction in present study may be related to low dose of 50mg/kg.

Conclusion

Intranasal midazolam showed better efficacy as compared to oral triclofos as procedural sedative in paediatric age group for non-invasive procedures as it had higher reactivity score, lesser post procedural sedation, lesser need of additional dose to complete the procedures.

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