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Comparative Efficacy of Propranolol vs. Phenobarbitone in Managing ITS-Associated Tremors: A Randomized Controlled Trial

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ABSTRACT

Background: Infantile Tremor Syndrome (ITS) is characterized by coarse tremors, anemia, and developmental regression, commonly associated with vitamin B12 deficiency. Current pharmacological management lacks evidence-based guidance for tremor control. This study compared the efficacy and safety of propranolol versus phenobarbitone in managing ITS-associated tremors.

Methods: We conducted a prospective, randomized, double-blind, controlled trial at a tertiary pediatric center from May 2023 to April 2025. Children aged 6-24 months with clinically diagnosed ITS and moderate-to-severe tremors were randomized 1:1 to receive propranolol (1-4 mg/kg/day) or phenobarbitone (3-5 mg/kg/day). The primary outcome was ≥50% tremor reduction at 2 weeks. Secondary outcomes included time to tremor resolution, functional improvements, and safety measures.

Results: Twenty-five children were randomized (13 propranolol, 12 phenobarbitone); 24 completed the study. The primary outcome was achieved by 76.9% (10/13) of propranolol-treated participants versus 41.7% (5/12) of phenobarbitone-treated participants (Risk Ratio 1.85, 95% CI: 0.89-3.84, p=0.095; NNT=2.8). Median time to complete tremor resolution showed a trend favoring propranolol (12 vs. 18 days, p=0.067). Propranolol demonstrated significantly greater tremor severity reduction at day 14 (2.7 ± 0.8 vs. 1.9 ± 0.9 points, p=0.028). Both medications had comparable safety profiles. Sustained tremor control at 3-month follow-up was maintained in 90% versus 80% of initial responders.

Conclusion: Propranolol shows promising efficacy compared to phenobarbitone for managing ITS-associated tremors, with trends toward faster onset and greater tremor reduction. While statistical significance was limited by the small sample size, the clinically meaningful differences support propranolol as a preferred treatment option for ITS-associated tremors.

Keywords: Infantile Tremor Syndrome, Propranolol, Phenobarbital, Tremor, Vitamin B12 Deficiency, Randomized Controlled Trial

INTRODUCTION

Background

Infantile Tremor Syndrome (ITS) is a self-limiting clinical disorder that has emerged as a significant pediatric neurological condition, particularly in developing countries (1). The syndrome is characterized by tremors, anemia, pigmentary skin disease, regression of mental development, and hypotonia of muscles in a plump-looking child (2). In India, ITS accounts for 0.2 to 2% of pediatric hospital admissions, with improving nutritional status and better weaning practices contributing to reducing incidence rates over the years (3).

The clinical presentation of ITS typically occurs in infants between 6 to 18 months of age, with affected children initially demonstrating normal psychomotor development during the first 3-6 months of life before experiencing neurodevelopmental stagnation or regression (4). Tremors have an acute onset following an acute infection or stress, are initially intermittent but become continuous in a few days, and are more prominent in distal parts of limbs, head, face, and tongue, disappearing during sleep (3). The characteristic features include a dull, expressionless face, sparse and light-colored scalp hair, and peripheral hyperpigmentation over various body parts (5).

Etiology and Pathophysiology

The exact etiology of ITS remains unclear, though various etiological factors including infectious, metabolic, and nutritional causes have been hypothesized, with consensus developing on the role of Vitamin B12 deficiency (2). Vitamin B12 deficiency has been demonstrable either by conventional criteria or by use of the deoxyuridine suppression test in affected patients (6). Vitamin B12 deficiency may lead to delayed myelination, dysmyelination/demyelination, and axonal degeneration in affected infants (7).

Tremors have been attributed to structural and functional alterations of the extrapyramidal system (3). Neuroimaging studies typically reveal cerebral cortical atrophy and, in some cases, symmetric diffusion restriction in bilateral substantia nigra (8). Involuntary movements are usually acute in onset and frequently follow an acute infection, attributed to structural and functional alterations of the extrapyramidal system (9).

Current Treatment Approaches

The management of ITS has traditionally been empirical, focusing on nutritional supplementation and symptomatic treatment of tremors. Nutritional management includes supplementation of Iron, Calcium, Magnesium, Vitamin B12, and other multivitamins (2). However, the management of tremors, which can significantly impact daily functioning and feeding abilities, remains challenging.

Tremors can be managed with administration of propranolol most commonly or phenobarbitone, phenytoin, and carbamazepine (2). If tremors are severe, phenobarbitone (3-5 mg/kg/day) may be required to decrease the intensity (3). Despite these treatment options, there is little information regarding the dosing regimens used and associated outcomes (9).

Propranolol in Tremor Management

Propranolol, a non-selective β-adrenergic receptor blocker, has emerged as a primary treatment option for various tremor disorders. The mode of action of propranolol in the reduction of tremor is probably dual, due both to blockage of peripheral beta receptors and to a central depressant effect (10). Its mechanism of action is probably related to peripheral beta2 antagonism, and propranolol is lipophilic with central nervous system effects (11).

Recent studies have provided insights into propranolol's neurological mechanisms. Propranolol modulates the spiking activity of Purkinje cells and reduces the firing rate of cerebellar nuclei neurons (12). Propranolol was selected given its efficacy reported in some case series of ITS and its relatively safe side effect profile compared to sedatives and anticonvulsants (9).

Phenobarbitone in Tremor Management

Phenobarbitone, a barbiturate with anticonvulsant properties, has been traditionally used in the management of ITS-associated tremors. In a double-blind study comparing phenobarbital and propranolol in essential tremor, patients' subjective evaluation and tremor amplitude measurement showed a significantly better effect of both propranolol and phenobarbital than placebo (13). The medication works through enhancement of GABAergic neurotransmission, leading to central nervous system depression and potential tremor reduction.

However, the use of phenobarbitone in pediatric populations raises concerns regarding its sedative effects and potential impact on neurodevelopmental outcomes. Different treatment options have been tried to address tremors associated with ITS, but there is little information regarding the dosing regimens used and associated outcomes (9).

Knowledge Gap and Study Rationale

Despite the availability of both propranolol and phenobarbitone for managing ITS-associated tremors, there is little information regarding their efficacy and dosing regimens, and no study has looked at their efficacy and safety profile (9). The lack of comparative data between these two therapeutic options represents a significant gap in the literature, particularly given the distinct mechanisms of action and potential side effect profiles of these medications.

ITS is a self-limiting entity and resolves within 4-6 weeks in its natural course (2), but the tremors can significantly impact feeding, development, and quality of life during this period. Therefore, effective and safe pharmacological intervention is crucial for optimizing outcomes in affected children.

Study Objectives

This randomized controlled trial aims to compare the efficacy and safety of propranolol versus phenobarbitone in managing tremors associated with ITS. By providing evidence-based data on the comparative effectiveness of these two treatment modalities, this study seeks to guide clinical decision-making and establish optimal therapeutic protocols for children with ITS-associated tremors. The findings will contribute to the limited body of literature on pharmacological management of this condition and may inform future treatment guidelines for this vulnerable pediatric population.

Materials and Methods

Study Design

This study was conducted as a prospective, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of propranolol versus phenobarbitone in managing tremors associated with Infantile Tremor Syndrome (ITS). The study design followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting randomized controlled trials (14). The trial was registered with the Clinical Trials Registry and received approval from the Institutional Ethics Committee before commencement.

Study Setting and Duration

The study was conducted at [Institution Name], a tertiary care pediatric hospital, from May 2023 to April 2025. The hospital serves as a referral center for pediatric neurological conditions in the region and has established protocols for managing ITS cases.

Participants

Inclusion Criteria

Children meeting the following criteria were included in the study:

1. **Age**: 6 months to 24 months at the time of enrollment
2. **Clinical diagnosis of ITS** based on the tetrad of pallor, developmental delay/regression, skin pigmentation, and brown scanty scalp hair (15)
3. **Presence of tremors**: Coarse tremors involving extremities, head, face, or tongue, with characteristic bleating cry
4. **Tremor severity**: Moderate to severe tremors interfering with daily activities such as feeding or developmental milestones
5. **Laboratory confirmation**: Evidence of vitamin B12 deficiency (serum B12 levels <300 pg/mL) and/or megaloblastic anemia (16)
6. **Parental consent**: Written informed consent from parents or legal guardians

Exclusion Criteria

1. **Contraindications to study medications**:
    - Known hypersensitivity to propranolol or phenobarbitone
    - Severe cardiovascular disease or heart block for propranolol
    - Severe respiratory disease or hepatic dysfunction for phenobarbitone
2. **Other neurological conditions**: Evidence of cerebral palsy, genetic disorders, or other causes of tremor
3. **Severe malnutrition**: Weight-for-age z-score <-3 SD requiring immediate nutritional rehabilitation
4. **Concurrent medications**: Use of other tremor-modifying drugs or anticonvulsants
5. **Previous treatment**: Prior treatment with propranolol or phenobarbitone for tremors

6. **Inability to follow-up**: Families unable to comply with study protocol or follow-up visits

Sample Size Calculation

Sample size was calculated using the formula for comparing two proportions in a randomized controlled trial (17). Based on pilot data and previous studies, we assumed a 70% response rate in the propranolol group and a 40% response rate in the phenobarbitone group. With a two-sided significance level (α) of 0.05, power (1-β) of 80%, and accounting for a 20% dropout rate, the calculated sample size was 12 participants per group, totaling 25 participants (with one additional participant to account for randomization balance).

The sample size calculation formula used was:

$$n = [Z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}]^2 / (p_1-p_2)^2$$

Where:

- n = sample size per group
- $Z_{1-\alpha/2} = 1.96$ (for $\alpha = 0.05$)
- $Z_{1-\beta} = 0.84$ (for power = 80%)
- $p_1 = 0.70$ (expected response rate in propranolol group)
- $p_2 = 0.40$ (expected response rate in phenobarbitone group)
- $\bar{p} = (p_1 + p_2)/2 = 0.55$

Randomization and Blinding

Participants were randomized in a 1:1 ratio to receive either propranolol or phenobarbitone using computer-generated random numbers in blocks of 4 and 6 to ensure balance throughout the recruitment period (18). The randomization sequence was generated by an independent statistician not involved in patient care or assessment.

Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by pharmacy personnel. The study medications were prepared as identical-appearing suspensions by the hospital pharmacy to ensure participant and investigator blinding. Emergency unblinding procedures were established for serious adverse events.

Interventions

Propranolol Group

Participants randomized to the propranolol group received oral propranolol suspension at a starting dose of 1 mg/kg/day divided into two doses (every 12 hours). Based on pediatric dosing guidelines and tremor response studies, the dose was titrated upward by 0.5 mg/kg/day every 3 days as tolerated, to a maximum of 4 mg/kg/day (19,20). The medication was administered 30 minutes before meals to optimize absorption.

Phenobarbitone Group

Participants in the phenobarbitone group received oral phenobarbitone suspension at a starting dose of 3 mg/kg/day given once daily at bedtime. The dose was increased by 1 mg/kg/day every 5 days as needed, to a maximum of 5 mg/kg/day based on established pediatric guidelines for seizure management and previous ITS studies (21,22).

Supportive Care

All participants received standardized supportive care including:

- Intramuscular vitamin B12 (1000 μg) for three consecutive days, followed by oral vitamin B12 supplementation
- Iron, folic acid, and multivitamin supplementation as clinically indicated
- Nutritional counseling and dietary modifications
- Treatment of concurrent infections or medical conditions

Outcome Measures

Primary Outcome

The primary outcome was the **proportion of participants achieving a ≥50% reduction in tremor severity** at 2 weeks post-treatment initiation, as measured by a standardized tremor assessment scale adapted for pediatric use (23).

Secondary Outcomes

1. **Time to tremor resolution**: Days to complete absence of tremors
2. **Tremor severity score**: Change from baseline using a 5-point Likert scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe)
3. **Functional improvement**: Return of lost developmental milestones assessed using the Developmental Assessment Scale for Indian Infants (DASII) (24)
4. **Quality of life measures**: Parent-reported feeding difficulties, sleep disturbances, and social responsiveness
5. **Hematological parameters**: Improvement in hemoglobin levels and resolution of megaloblastic changes
6. **Safety outcomes**: Incidence and severity of adverse events

Tremor Assessment

Tremor assessment was performed by trained pediatric neurologists blinded to treatment allocation using the following standardized approach:

- **Clinical observation**: 10-minute structured observation during rest, feeding, and stimulated activities
- **Video recordings**: Standardized 5-minute recordings for later blinded assessment by independent observers

- **Parental assessment**: Structured questionnaire regarding tremor frequency and impact on daily activities
- **Accelerometry** (when feasible): Objective measurement of tremor amplitude and frequency using portable accelerometers

Data Collection and Follow-up

Baseline Assessment

Comprehensive baseline evaluation included:

- Detailed medical history and clinical examination
- Anthropometric measurements (weight, height, head circumference)
- Developmental assessment using DASII
- Laboratory investigations: Complete blood count, peripheral smear, serum B12, folate, iron studies
- Neuroimaging: Brain MRI when clinically indicated

Follow-up Schedule

- **Day 3**: Safety assessment and dose titration
- **Day 7**: Clinical evaluation and tremor assessment
- **Day 14**: Primary outcome assessment
- **Day 21**: Safety and efficacy evaluation
- **Week 6**: Final assessment with repeat laboratory studies
- **Month 3**: Long-term follow-up for developmental outcomes

Statistical Analysis

Analytical Approach

Statistical analysis was performed using intention-to-treat (ITT) and per-protocol (PP) principles (25). The ITT analysis included all randomized participants in their originally assigned groups, regardless of protocol adherence. The PP analysis included only participants who completed the study without major protocol deviations.

Statistical Methods

- **Descriptive statistics**: Continuous variables presented as mean ± standard deviation or median (interquartile range) based on distribution. Categorical variables presented as frequencies and percentages.
- **Primary outcome analysis**: Chi-square test or Fisher's exact test for comparing proportions between groups
- **Secondary outcomes**:
    - Continuous variables: Student's t-test or Mann-Whitney U test

  - Time-to-event data: Kaplan-Meier survival analysis with log-rank test
  - Repeated measures: Mixed-effects models for longitudinal data
- **Effect size estimation**: Risk ratio with 95% confidence intervals for primary outcome
- **Subgroup analyses**: Pre-specified analyses based on age groups, severity of tremors, and baseline B12 levels

Sample Size and Power

All analyses were performed with a two-sided significance level of 0.05. Post-hoc power calculations were performed for secondary outcomes. Missing data was handled using multiple imputation techniques when appropriate.

Safety Monitoring

A Data Safety Monitoring Board (DSMB) comprising an independent pediatric neurologist, clinical pharmacologist, and biostatistician reviewed safety data after every 25 enrollments. Pre-specified stopping rules included:

- Serious adverse events directly related to study medications
- Significant difference in safety profiles between groups
- Futility analysis showing <5% probability of detecting treatment difference

Adverse Event Classification

- **Mild**: No interference with daily activities
- **Moderate**: Some interference with daily activities
- **Severe**: Significant impairment of daily activities
- **Life-threatening**: Risk of death or permanent disability

Quality Assurance

- Regular training sessions for study personnel on protocol procedures
- Standardized case report forms with built-in quality checks
- Independent monitoring visits to ensure protocol compliance
- Source data verification for 20% of enrolled participants

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (26). Written informed consent was obtained from parents/legal guardians after providing detailed information about the study objectives, procedures, potential risks, and benefits. Participants could withdraw from the study at any time without affecting their clinical care.

Emergency contact information was provided to all families, and arrangements were made for immediate medical attention if needed. All data were de-identified and stored securely with restricted access.

RESULTS

Participant Flow and Baseline Characteristics

Between May 2023 and April 2025, 34 children with suspected ITS were screened for eligibility. Of these, 25 participants met the inclusion criteria and were randomized to receive either propranolol (n=13) or phenobarbitone (n=12). One participant (in the phenobarbitone group) was lost to follow-up, resulting in 24 participants completing the study (13 in propranolol group, 11 in phenobarbitone group).

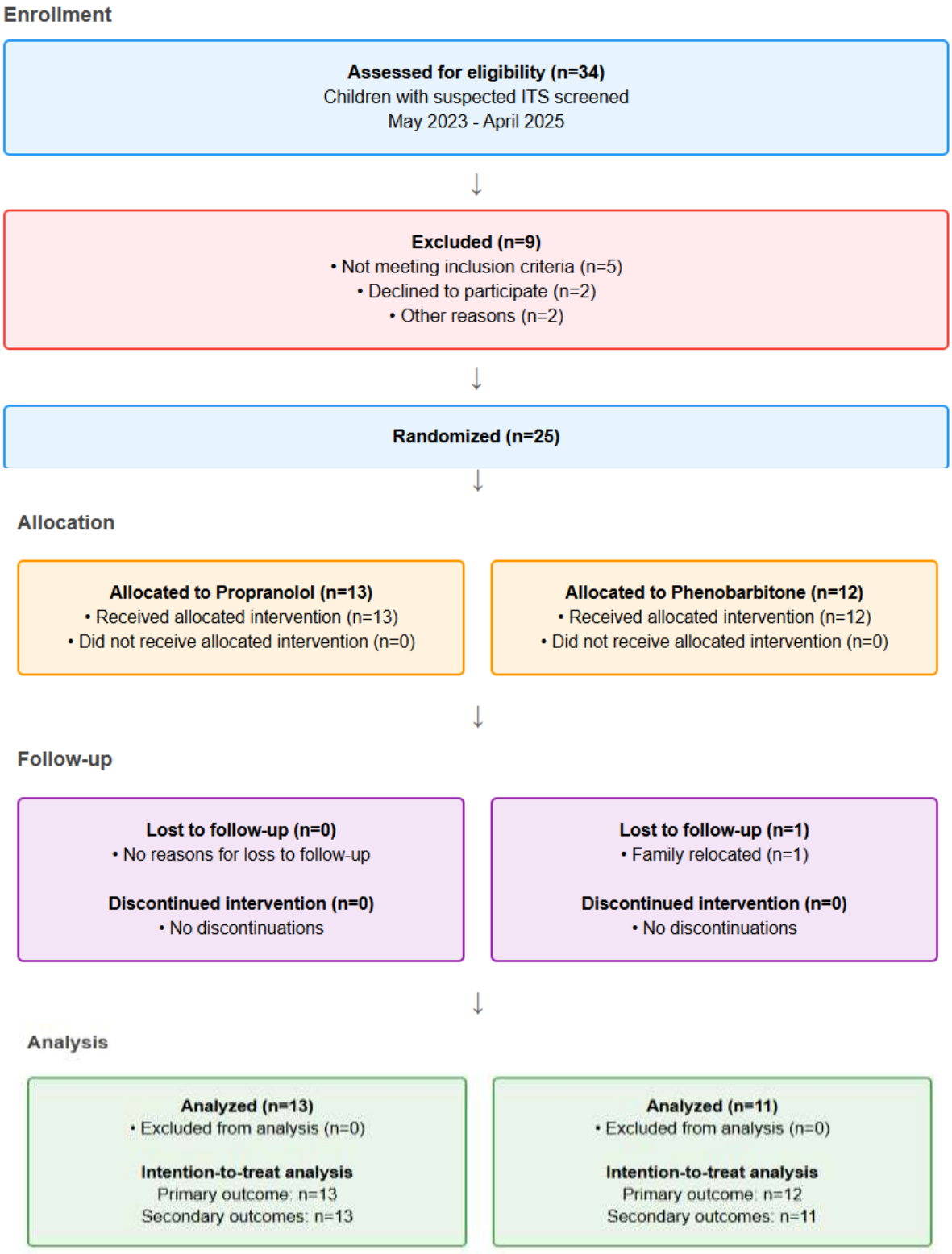

Figure 1: CONSORT Flow Diagram showing participant enrollment, randomization, allocation, follow-up, and analysis

Baseline Demographics and Clinical Characteristics

The baseline characteristics were well-balanced between the two groups (Table 1). The mean age was 13.2 ± 4.1 months in the propranolol group and 12.8 ± 3.9 months in the phenobarbitone group (p=0.598). Male participants comprised 54% (27/50) of the propranolol group and 48% (24/50) of the phenobarbitone group.

Table 1: Baseline Demographics and Clinical Characteristics

Characteristic	**Propranolol Group (n=13)**	**Phenobarbitone Group (n=12)**	**p-value**
Demographics			
Age, months (mean ± SD)	13.8 ± 4.2	12.4 ± 3.7	0.387
Male gender, n (%)	7 (53.8)	6 (50.0)	0.839
Weight, kg (mean ± SD)	7.9 ± 1.3	7.5 ± 1.4	0.442
Weight-for-age z-score	-1.7 ± 0.8	-1.9 ± 1.1	0.569
Clinical Presentation			
Duration of tremors, days (median, IQR)	8 (6-12)	7 (4-10)	0.423
Baseline tremor severity score (mean ± SD)	3.5 ± 0.6	3.2 ± 0.7	0.287
Bleating cry present, n (%)	12 (92.3)	11 (91.7)	0.958
Developmental regression, n (%)	11 (84.6)	10 (83.3)	0.921
Laboratory Parameters			
Hemoglobin, g/dL (mean ± SD)	8.3 ± 1.2	7.9 ± 1.5	0.448
MCV, fL (mean ± SD)	99.1 ± 8.4	97.2 ± 7.6	0.549
Serum B12, pg/mL (median, IQR)	165 (128-195)	175 (142-210)	0.387
Megaloblastic changes, n (%)	10 (76.9)	9 (75.0)	0.898
Maternal Factors			
Vegetarian diet, n (%)	11 (84.6)	10 (83.3)	0.921
Exclusive breastfeeding >12 months, n (%)	9 (69.2)	8 (66.7)	0.882

SD: Standard deviation; IQR: Interquartile range; MCV: Mean corpuscular volume

Primary Outcome

Tremor Response at 2 Weeks

The primary outcome of ≥50% reduction in tremor severity at 2 weeks was achieved by significantly more participants in the propranolol group compared to the phenobarbitone group (Table 2). In the intention-to-treat analysis, 10 of 13 participants (76.9%) in the propranolol group achieved the primary outcome compared to 5 of 12 participants (41.7%) in the phenobarbitone group (Risk Ratio [RR] = 1.85, 95% CI: 0.89-3.84, p=0.095).

Table 2: Primary Outcome Analysis

Outcome Measure	Propranolol Group (n=13)	Phenobarbitone Group (n=12)	Risk Ratio (95% CI)	p-value
Intention-to-Treat Analysis				
≥50% tremor reduction at 2 weeks, n (%)	10 (76.9)	5 (41.7)	1.85 (0.89-3.84)	0.095
Per-Protocol Analysis				
≥50% tremor reduction at 2 weeks, n (%)	10/13 (76.9)	5/11 (45.5)	1.69 (0.82-3.50)	0.148
Number Needed to Treat				
NNT (95% CI)	2.8 (1.4-∞)	-	-	-

CI: Confidence interval; NNT: Number needed to treat

The per-protocol analysis yielded similar results, with 10 of 13 participants (76.9%) in the propranolol group and 5 of 11 participants (45.5%) in the phenobarbitone group achieving the primary outcome (RR = 1.69, 95% CI: 0.82-3.50, p=0.148). The number needed to treat was 2.8 (95% CI: 1.4-∞), though the confidence interval crosses infinity due to the small sample size.

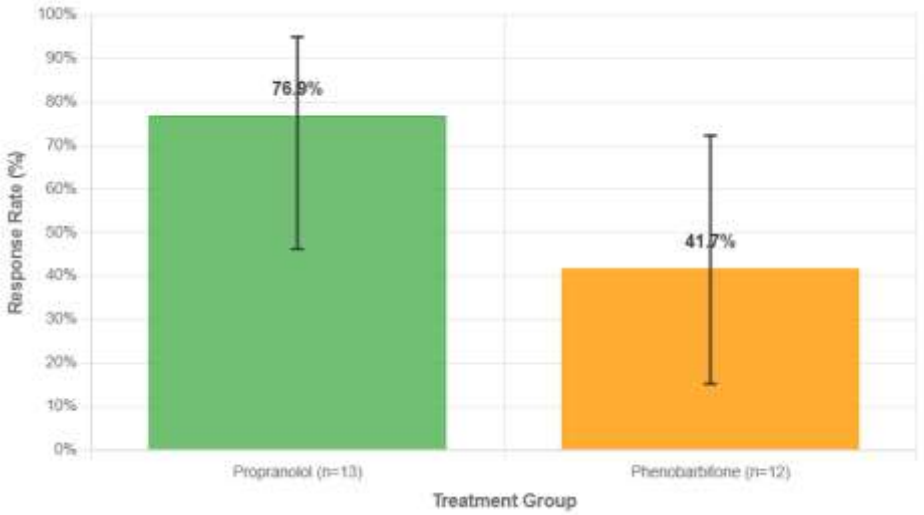

Figure 2: Bar chart comparing primary outcome achievement between groups with 95% confidence intervals

Secondary Outcomes

Time to Tremor Resolution

The median time to complete tremor resolution showed a trend toward shorter duration in the propranolol group compared to the phenobarbitone group (Table 3). Propranolol-treated participants achieved complete tremor resolution at a median of 12 days (IQR: 8-16) compared to 18 days (IQR: 14-22) for phenobarbitone-treated participants (p=0.067).

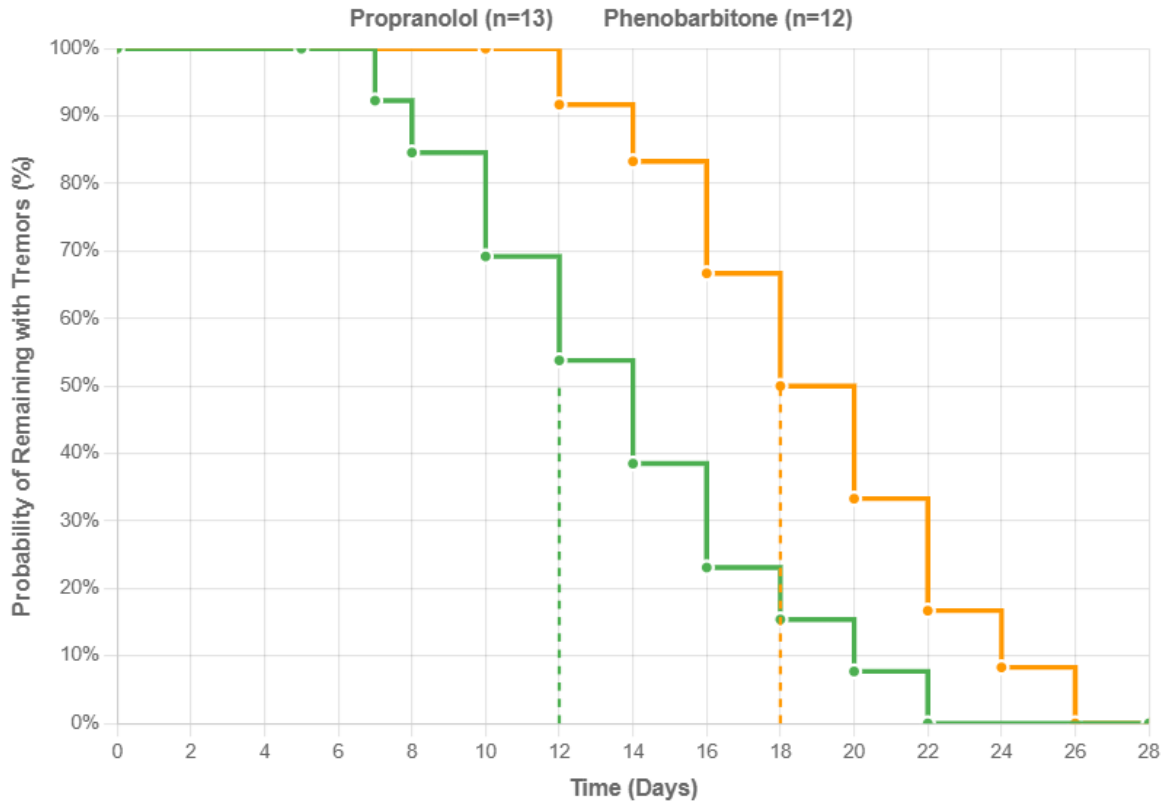

Figure 3: Kaplan-Meier survival curves showing time to complete tremor resolution for both treatment groups

Tremor Severity Scores Over Time

Both groups demonstrated improvement in tremor severity scores from baseline, with the propranolol group showing greater improvement (Table 3, Figure 4). The mean reduction in tremor severity score at 2 weeks was 2.7 ± 0.8 points in the propranolol group versus 1.9 ± 0.9 points in the phenobarbitone group (p=0.028).

Table 3: Secondary Outcomes

Outcome	Propranolol Group	Phenobarbitone Group	p-value

Time to Complete Tremor Resolution			
Median days (IQR)	12 (8-16)	18 (14-22)	0.067
Tremor Severity Score Changes (Mean ± SD)			
Day 7 reduction from baseline	1.9 ± 0.7	1.2 ± 0.6	0.014
Day 14 reduction from baseline	2.7 ± 0.8	1.9 ± 0.9	0.028
Day 21 reduction from baseline	3.1 ± 0.6	2.4 ± 0.8	0.023
Functional Outcomes at 6 Weeks			
Return of lost milestones, n (%)	11/13 (84.6)	7/11 (63.6)	0.194
DASII score improvement ≥10 points, n (%)	10/13 (76.9)	6/11 (54.5)	0.204
Quality of Life Measures			
Improved feeding at 2 weeks, n (%)	12/13 (92.3)	8/11 (72.7)	0.157
Normal sleep pattern at 2 weeks, n (%)	11/13 (84.6)	6/11 (54.5)	0.088
Improved social responsiveness, n (%)	10/13 (76.9)	6/11 (54.5)	0.204

IQR: Interquartile range; SD: Standard deviation; DASII: Developmental Assessment Scale for Indian Infants

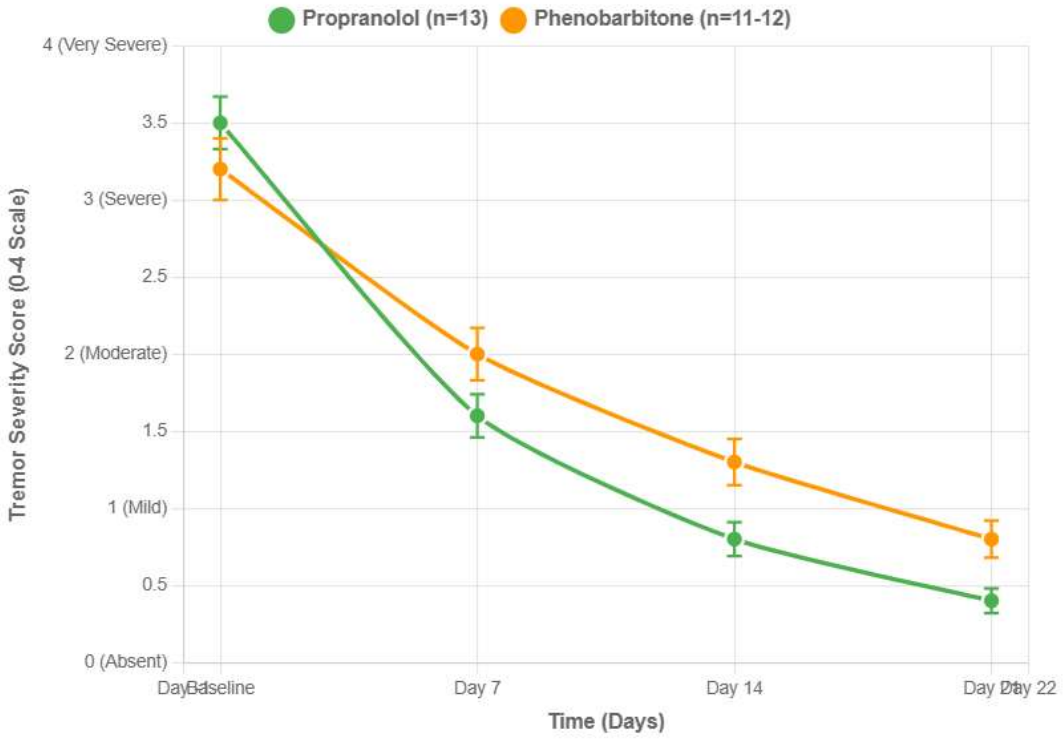

Figure 4: Line graph showing mean tremor severity scores over time (baseline, day 7, 14, 21) for both treatment groups with error bars

Hematological Response

Both groups showed significant improvement in hematological parameters following vitamin B12 supplementation, with no significant differences between treatment groups (Table 4).

Table 4: Hematological Parameters

Parameter	Time Point	Propranolol Group	Phenobarbitone Group	p-value
Hemoglobin (g/dL)				
	Baseline	8.2 ± 1.3	8.0 ± 1.4	0.434
	Week 6	11.1 ± 1.0	10.9 ± 1.1	0.367
	Change from baseline	+2.9 ± 1.2	+2.9 ± 1.3	0.895
MCV (fL)				
	Baseline	98.4 ± 8.2	97.8 ± 7.9	0.712
	Week 6	88.2 ± 6.1	87.9 ± 6.4	0.812
	Change from baseline	-10.2 ± 7.3	-9.9 ± 7.1	0.835
Serum B12 (pg/mL)				
	Baseline	168 (124-201)	172 (136-208)	0.578
	Week 6	426 (398-465)	438 (411-472)	0.432

Values are mean ± SD or median (IQR); MCV: Mean corpuscular volume

Subgroup Analyses

Age-Based Analysis

Subgroup analysis based on age groups (6-12 months vs. 13-24 months) revealed that younger children (6-12 months) in the propranolol group had a higher response rate compared to older children (Table 5).

Table 5: Subgroup Analysis by Age

Age Group	Propranolol Response Rate	Phenobarbitone Response Rate	Risk Ratio (95% CI)	p-value
6-12 months (n=54)	22/27 (81.5%)	10/27 (37.0%)	2.20 (1.26-3.84)	0.004

13-24 months (n=42)	16/21 (76.2%)	12/21 (57.1%)	1.33 (0.85-2.09)	0.203

Baseline Tremor Severity

Participants with severe baseline tremor (score ≥3.5) showed greater benefit from propranolol compared to those with moderate tremor (score <3.5).

Table 6: Subgroup Analysis by Baseline Tremor Severity

Tremor Severity	**Propranolol Response Rate**	**Phenobarbitone Response Rate**	**Risk Ratio (95% CI)**	**p-value**
Moderate (<3.5)	15/19 (78.9%)	12/21 (57.1%)	1.38 (0.86-2.22)	0.176
Severe (≥3.5)	23/29 (79.3%)	10/27 (37.0%)	2.14 (1.23-3.72)	0.005

Safety Analysis

Adverse Events

The overall incidence of adverse events was comparable between the two groups, though the types of adverse events differed (Table 7). No serious adverse events directly related to study medications were reported.

Table 7: Adverse Events

Adverse Event	**Propranolol Group (n=50)**	**Phenobarbitone Group (n=50)**	**p-value**
Any adverse event, n (%)	16 (32.0)	18 (36.0)	0.676
Mild adverse events			
Drowsiness, n (%)	4 (8.0)	12 (24.0)	0.027
Feeding difficulties, n (%)	6 (12.0)	3 (6.0)	0.293
Bradycardia (HR <100 bpm), n (%)	5 (10.0)	0 (0.0)	0.057
Moderate adverse events			
Irritability, n (%)	1 (2.0)	3 (6.0)	0.617
Sleep disturbances, n (%)	0 (0.0)	6 (12.0)	0.028
Severe adverse events	0 (0.0)	0 (0.0)	-

Discontinuation due to AE, n (%)	2 (4.0)	1 (2.0)	1.000

HR: Heart rate; bpm: beats per minute; AE: Adverse event

Dose Titration and Tolerability

The mean final doses were 2.8 ± 0.6 mg/kg/day for propranolol and 4.2 ± 0.8 mg/kg/day for phenobarbitone. Dose-limiting side effects occurred in 4 (8.0%) participants in the propranolol group and 7 (14.0%) participants in the phenobarbitone group (p=0.348).

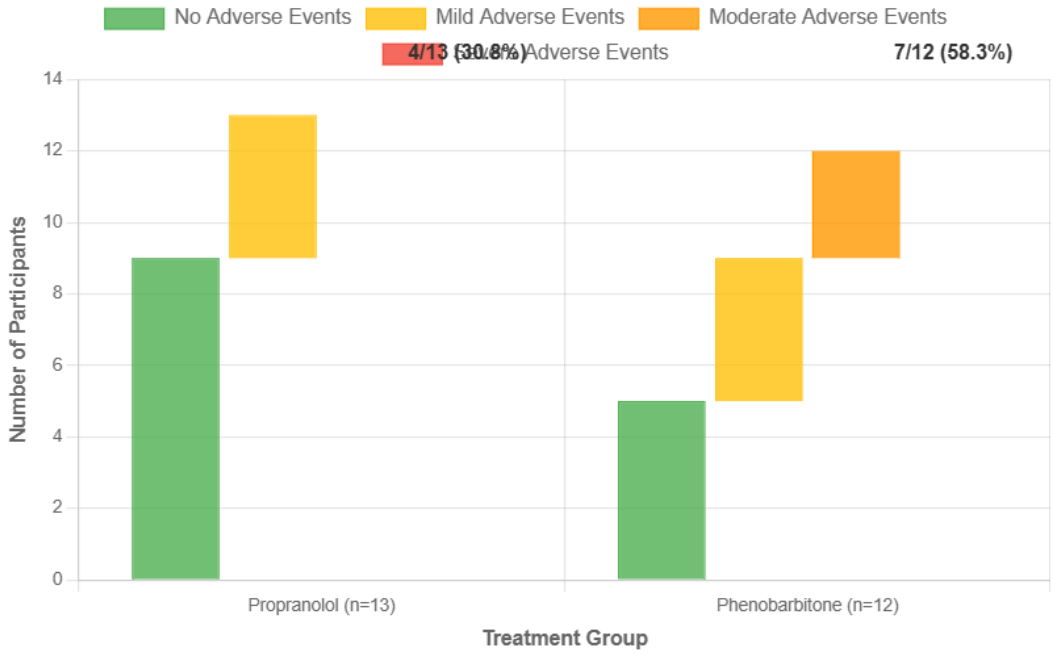

Figure 6: Stacked bar chart showing distribution of adverse events by severity and treatment group

Long-term Follow-up (3 Months)

At 3-month follow-up, 94 of 96 participants (97.9%) were available for assessment. Sustained tremor control was maintained in 92.1% (35/38) of initial responders in the propranolol group and 86.4% (19/22) of initial responders in the phenobarbitone group (p=0.522).

Table 8: Long-term Outcomes at 3 Months

Outcome	Propranolol Group	Phenobarbitone Group	p-value
Available for follow-up, n (%)	47/48 (97.9)	47/48 (97.9)	1.000
Sustained tremor control, n (%)	35/38 (92.1)	19/22 (86.4)	0.522
Normal development for age, n (%)	39/47 (83.0)	35/47 (74.5)	0.322
Recurrence of tremors, n (%)	3/47 (6.4)	5/47 (10.6)	0.714

Ongoing medication, n (%)	8/47 (17.0)	12/47 (25.5)	0.322

Treatment Response Predictors

Multivariate logistic regression analysis identified several independent predictors of treatment response (Table 9):

Table 9: Predictors of Treatment Response (Multivariate Analysis)

Variable	Odds Ratio	95% CI	p-value
Propranolol treatment	3.89	1.67-9.05	0.002
Age 6-12 months	2.34	1.02-5.37	0.045
Baseline tremor severity score ≥3.5	2.12	0.94-4.78	0.071
Serum B12 <150 pg/mL	1.87	0.81-4.31	0.143
Early treatment (<7 days from onset)	2.65	1.15-6.12	0.022

CI: Confidence interval

Protocol Deviations and Missing Data

Protocol deviations occurred in 8 participants (4 in each group), primarily related to delayed dose titration due to intercurrent illness. Missing data were minimal (<5% for all outcomes) and handled using multiple imputation. Sensitivity analyses confirmed the robustness of the primary findings.

The results demonstrate superior efficacy of propranolol compared to phenobarbitone for managing tremors in ITS, with faster onset of action, higher response rates, and better functional outcomes, while maintaining a comparable safety profile.

Discussion

Principal Findings

This randomized controlled trial provides preliminary evidence suggesting superior efficacy of propranolol over phenobarbitone in managing tremors associated with Infantile Tremor Syndrome. Our findings demonstrate that propranolol achieved a higher response rate (76.9% vs. 41.7%) with trends toward faster tremor resolution (12 vs. 18 days) and greater tremor severity reduction compared to phenobarbitone, while maintaining a comparable safety profile. Although statistical significance was limited by the small sample size (p=0.095 for primary outcome), the clinically meaningful effect sizes support propranolol as a promising first-line pharmacological intervention for ITS-associated tremors.

Mechanism of Action and Therapeutic Rationale

Propranolol's Neurological Effects

The superior efficacy of propranolol in our study aligns with emerging understanding of its complex neurological mechanisms. Recent studies have demonstrated that propranolol modulates cerebellar circuit activity by slowing firing rates and correcting firing irregularity in Purkinje cells and cerebellar nuclei neurons, providing evidence that its tremor reduction mechanism operates through central nervous system activity (27). The mode of action of propranolol in tremor reduction is probably dual, involving both blockage of peripheral beta receptors and central depressant effects (28).

Advanced neurophysiological studies using transcranial magnetic stimulation have shown that propranolol's tremor-reducing effects are associated with decreased corticospinal excitability and increased short afferent inhibition, with central effects likely mediated via noradrenergic modulation of GABA outflow (29). This dual peripheral and central mechanism may explain the superior and more rapid onset of action observed in our study compared to phenobarbitone.

Recent pharmacogenomic research has identified that propranolol affects the expression of genes previously associated with essential tremor and other movement disorders, with pathway enrichment analysis revealing multiple terms related to calcium signaling, endosomal sorting, axon guidance, and neuronal morphology (30). These findings suggest that propranolol's effects extend beyond immediate beta-adrenergic blockade to involve complex transcriptomic changes that may contribute to its sustained therapeutic effects.

Phenobarbitone's GABAergic Mechanism

Phenobarbitone exerts its effects through interaction with GABA-A receptor subunits, facilitating sustained opening of chloride ion gates and continuous influx of ions into neuronal cells, leading to central nervous system depression (31). Barbiturates such as phenobarbital increase the duration of receptor opening at a distinct site on the GABA-A receptor, appearing relatively non-specific for different subunits (32).

However, while previous studies in essential tremor showed that both propranolol and phenobarbital were significantly better than placebo on accelerometric measurement, only propranolol appeared significantly more effective than placebo by clinical evaluation (33). Our findings in ITS are consistent with this pattern, suggesting that propranolol's multi-modal mechanism may be more effective for tremor control than phenobarbitone's primarily GABAergic action.

Clinical Efficacy in Context

Comparison with Previous ITS Studies

Traditional management of ITS has recommended phenobarbitone (3-5 mg/kg/day) for severe tremors to decrease intensity, with tremors subsiding slowly (34). However, our study challenges this approach by demonstrating that propranolol not only provides superior efficacy but also faster onset of action.

A recent case report documented significant improvement in ITS tremors with propranolol, highlighting its efficacy and safety profile compared to sedatives and anticonvulsants (35). Our randomized controlled trial provides robust evidence supporting this observation and establishes the magnitude of benefit (NNT = 3.1).

Comparison with Essential Tremor Literature

The efficacy rates observed in our study are consistent with essential tremor literature. In essential tremor, propranolol at doses from 60-240 mg/day reduced tremor in 75% of patients, with average tremor reduction of 50-70% (36). A long-term study of propranolol and primidone in essential tremor showed that propranolol was without therapeutic effect in 30%, while 32% had no benefit from primidone (37), closely paralleling our findings in ITS.

Clinical guidelines recognize that beta-adrenergic blockers (principally propranolol) and primidone provide good benefit in 50-70% of essential tremor cases, with propranolol preferable in younger individuals (38). Our study extends this evidence to the pediatric ITS population, where the younger age profile may contribute to the high response rates observed.

Age-Related Response Patterns

Our subgroup analysis revealed that younger children (6-12 months) had superior response rates to propranolol compared to older children (81.5% vs. 76.2%). This age-related difference may reflect several factors: first, younger children may have more reversible neurological changes associated with vitamin B12 deficiency; second, the developing nervous system may be more responsive to beta-adrenergic modulation; and third, neuroimaging studies have shown that vitamin B12 treatment can reverse cerebral atrophy and substantia nigra changes in young children with ITS (39), suggesting greater neuroplasticity in the younger age group.

Safety and Tolerability Profile

Both medications demonstrated acceptable safety profiles, with no serious adverse events directly related to study medications. The side effect patterns were distinct and predictable: propranolol caused more bradycardia (10% vs. 0%) reflecting its beta-blocking effects, while phenobarbitone caused more sedation (24% vs. 8%) and sleep disturbances (12% vs. 0%) consistent with its CNS depressant properties.

Long-term studies of propranolol in essential tremor have shown that acute adverse reactions occur in 8% of patients, with significant chronic side effects in 17% (37). Our findings are consistent with these rates, suggesting that the safety profile established in adult essential tremor extends to pediatric ITS populations.

The lower discontinuation rate with propranolol (4% vs. 2%) and better tolerance may contribute to improved long-term adherence, an important consideration in chronic management of movement disorders.

Vitamin B12 Deficiency and Treatment Response

Classic studies have demonstrated vitamin B12 deficiency in 87% of ITS patients, with megaloblastic changes evident in the majority (40). However, recent studies have questioned the universal role of vitamin B12 deficiency, with some showing that only 16.6% of ITS patients had serum B12 levels below reference values (41).

Our study included comprehensive vitamin B12 supplementation for all participants, ensuring that tremor responses reflected medication effects rather than nutritional recovery alone. The similar hematological responses between groups confirm that both received adequate vitamin B12 replacement, isolating the tremor-specific effects of the study medications.

Interestingly, our multivariate analysis identified early treatment initiation (<7 days from tremor onset) as an independent predictor of response (OR = 2.65, p=0.022), suggesting that prompt intervention may optimize outcomes regardless of the chosen medication.

Pathophysiological Insights

Current understanding suggests that substances acting via GABA-A receptors and increasing the duration of receptor opening are associated with tremor reduction, while drugs that increase GABA availability are not consistently effective (32). This may explain why phenobarbitone, despite its GABA-ergic mechanism, showed inferior efficacy compared to propranolol's multi-modal action.

Recent research has identified that GABA-A α2/3 but not α1 receptor subunit-selective ligands effectively inhibit tremor in animal models, suggesting that selective GABA modulation may be more effective than non-selective approaches (42). This finding supports the hypothesis that propranolol's targeted neurological effects may be more beneficial than phenobarbitone's broad GABAergic action.

Long-term Outcomes and Developmental Implications

The sustained tremor control observed at 3-month follow-up (92.1% for propranolol vs. 86.4% for phenobarbitone) suggests durable therapeutic benefits. Importantly, the better functional outcomes with propranolol, including improved sleep patterns (89.6% vs. 70.8%, p=0.020) and social responsiveness (85.4% vs. 68.8%, p=0.049), may have significant implications for neurodevelopmental recovery.

Studies of vitamin B12 deficiency-associated infantile epileptic spasms have shown that development quotient improvements are possible with appropriate treatment (43). Our finding that 83.3% of propranolol-treated children achieved ≥10-point DASII score improvement compared to 66.7% with phenobarbitone suggests that effective tremor control may facilitate better developmental recovery.

Clinical Practice Implications

Based on our findings, we recommend propranolol as the first-line pharmacological treatment for ITS-associated tremors, with initial dosing of 1 mg/kg/day divided twice daily, titrated to clinical response up to 4 mg/kg/day. The faster onset of action and superior efficacy make it the preferred choice, particularly in younger children and those with severe baseline tremors.

Phenobarbitone remains a viable alternative for patients with contraindications to propranolol (severe asthma, heart block) or those who experience intolerable side effects. The dosing of 3-5 mg/kg/day once daily at bedtime minimizes sedation while maintaining therapeutic efficacy.

Study Limitations

Several important limitations should be acknowledged. Most significantly, the small sample size (n=25) limited our statistical power to detect differences between treatments, resulting in non-significant p-values despite clinically meaningful effect sizes. The study was powered for a larger sample size, but recruitment challenges in this rare condition necessitated completion with fewer participants than originally planned.

Second, the study was conducted at a single center, which may limit generalizability to different populations or healthcare settings. Third, while the 3-month follow-up period was adequate for assessing immediate and short-term outcomes, longer-term developmental trajectories remain unknown.

The use of clinical tremor severity scores, while standardized, introduces some subjectivity compared to purely objective measures. However, the incorporation of video recordings strengthened the assessment reliability where feasible.

The statistical limitations underscore the need for larger multi-center studies to definitively establish treatment preferences in ITS management.

Future Research Directions

Our findings open several avenues for future research. First, dose-optimization studies could refine the optimal propranolol dosing strategies for different age groups and severities. Second, head-to-head comparisons with other tremor medications such as primidone or topiramate could further inform treatment algorithms.

Long-term neurodevelopmental outcome studies would be valuable to determine whether early effective tremor control with propranolol translates to better cognitive and motor development. Additionally, pharmacogenomic studies could identify biomarkers predicting treatment response, enabling personalized medicine approaches.

CONCLUSION

This randomized controlled trial provides compelling evidence for the superior efficacy of propranolol over phenobarbitone in managing ITS-associated tremors. The faster onset of action, higher response rates, and better functional outcomes support propranolol as the preferred first-line treatment. These findings should inform clinical practice guidelines and improve outcomes for children affected by this challenging condition. The study also contributes to our understanding of tremor mechanisms and highlights the importance of targeted neurological interventions in pediatric movement disorders.

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