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INTERMITTENT DIAZEPAM AND CONTINUOUS PHENOBARBITAL TO TREAT RECURRENCE OF FEBRILE SEIZURES

A systematic review with meta-analysis

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ABSTRACT - Convulsions triggered by fever are the most common type of seizures in childhood, and 20% to 30% of them have recurrence. The prophylactic treatment is still controversial, so we performed a systematic review to find out the effectiveness of continuous phenobarbital and intermittent diazepam compared to placebo for febrile seizure recurrence. *Method:* Only randomized, double-blind, placebo-controlled trials were analyzed. The recurrence of febrile seizure was assessed for each drug. *Results:* Ten eligible clinical trials were included. Febrile seizure recurrence was smaller in children treated with diazepam or phenobarbital than in placebo group. Prophylaxis with either phenobarbital or diazepam reduces recurrences of febrile seizures. The studies were clinical, methodological, and statistically heterogeneous. *Conclusion:* The effectiveness of phenobarbital and diazepam could not be demonstrated because clinical trials were heterogeneous, and the recommendation for treatment recurrence should rely upon the experience of the assistant physician yet.

KEY WORDS: prophylactic treatment, febrile seizures, intermittent diazepam, continuous phenobarbital.

Diazepam intermitente e fenobarbital contínuo para tratamento da recorrência de convulsões febris: uma revisão sistemática com metanálise

RESUMO - As convulsões desencadeadas por febre são muito comuns na infância e 20% a 30% delas apresentam recorrência. O tratamento profilático, no entanto, ainda é controverso, motivo porque realizamos uma revisão sistemática para avaliar a eficácia do tratamento da recidiva de convulsão febril com diazepam e fenobarbital comparados a placebo. *Método*: Analisamos somente estudos randomizados, duplo-cegos, controlados, utilizando fenobarbital contínuo ou diazepam intermitente versus placebo. *Resultados*: Dez ensaios clínicos foram incluídos. A recorrência de convulsão febril foi menor no grupo das crianças tratadas com diazepam ou fenobarbital em relação ao controle. Tanto diazepam quanto fenobarbital reduziram as recorrências da convulsão febril. Os estudos foram clínica, metodológica e estatisticamente heterogêneos. *Conclusão*: A eficácia do fenobarbital e diazepam não pôde ser demonstrada nesta metanálise por causa da heterogeneidade dos ensaios clínicos, e a recomendação para tratamento de recorrência deve basear-se na experiência clínica de cada médico.

PALAVRAS-CHAVE: tratamento profilático, convulsões febris, diazepam intermitente, fenobarbital contínuo.

Febrile seizures are the most prevalent type of seizure, occurring in about 2% to 5% of young children, and their recurrence varies from 20% to 30%[1]. Febrile seizure is defined as convulsions occurring in children aged 0 to 5 years, with no history of neuropsychiatric disorders or with a concomitant neurological disease. The prognosis is good for the most patients, but seizures are upsetting to the children and parents. There are studies demonstrating a relation between the number of febrile seizures, mainly the complex ones, and the risk for epilepsy[2-3]. Besides, recurrent convulsions may be deleterious to intellectual development[4].

The prevention of febrile seizures might be benefi-

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cial, but the long-term management is controversial[5-7]. For some authors, prophylactic use of continuous phenobarbital prevents recurrence[8]. Others consider it of limited or no prophylactic value[9]. But they agree that side-effects and no compliance are common[3,9-10]. Also intermittent diazepam prophylaxis has been used, but this treatment is not worldwide accepted and it has been argued that intermittent prophylaxis often fails[11].

A review of trials published in English showed that only phenobarbital or valproate has effect in preventing febrile seizures recurrence and besides the results, those drugs were not recommended because of adverse effects. We performed a systematic review including trials published in English and also in Spanish and Portuguese to analyze the recurrence of febrile seizure in children treated with phenobarbital/diazepam and placebo.

METHOD

The electronic search was performed combining the following key words: febrile convulsion, febrile seizures, convulsão febril, crisis febriles, convulsión febril, phenobarbital, fenobarbital, diazepam and prophylaxis, profilaxia, profilaxis. The reference research was obtained from Cochrane Center of Brazil, Medline, Lilacs and Embase. Other research sources were from letters to experts, thesis indexed at BIREME/PAHO-WHO (Biblioteca Regional Medicina/Panamerican Health Organization of the World Health Organization), abstracts sent to Medical Meetings, but not published. We also have searched over the reference list of all recovered trials.

Classification of the trials. We classified the trials according to the randomization in A (described as randomized, description presented), B (described as randomized, description absent) and C (described as randomized, description present contrary evidence). Taking in account the blinding procedure we classified the studies in A (described as double-blind, description present), B (described as double-blind, description absent) and C (described as double-blind, description present contrary evidence).

We included in this systematic review only placebo controlled trials, with all sample sizes, classified as A or B for randomization, A or B for blinding, written in English, Portuguese and Spanish. We excluded in this review case reports and trials classified as C for randomization and C for blinding. We analysed the treatment in three ways: intermittent diazepam compared to placebo; continuous phenobarbital compared to placebo; intermittent diazepam or continuous phenobarbital compared to placebo.

Statistical Analysis. The analysis was performed in table 2X2: febrile seizure recurrence (yes or no) and the intermittent use of diazepam (yes or no); febrile convulsion recurrence (yes or no) and the use of continuous phenobarbital (yes or no). The statistical heterogeneity of the results was evaluated in funnel plot graphics, related to sample size (Y axis) and calculation of χ^2 test, in the N degrees of freedom, considering N = number of trials minus 1. To decide for a statistical significant finding it was used $\alpha < 5\%$.

RESULTS

We identified forty-eight trials published in English related to continuous use of phenobarbital and intermittent use of diazepam in the treatment of recurrences of febrile seizures. Thirty-eigth trials were excluded, for they were not randomized ones. Ten randomized clinical trials in English were initially included in this review, for they fulfilled the inclusion criteria. Thirty-five trials in Portuguese and Spanish were found and among them only one was eligible.

Among those eleven trials[2,4,6,12-19] classified (Table 1), one trial (Knudsen[12]) was subsequently excluded from our statistical analysis, because of the classification C for randomization.

Diazepam versus placebo. Comparing the treatment with diazepam *versus* placebo (Figure 1), the recurrence risk in febrile convulsion is lower in children treated with intermittent diazepam (NNT 17; 95% CI 10 to 85; $z=2.47$ $p<0.01$). So for each 17 treated children, one has no recurrence (OR for recurrence 0.6; 95% CI 0.40 to 0.90). In the diazepam group 11.2% (44/393) have recurrence and also 17.1% (68/398) of the placebo group. The results comparing the trials with diazepam and placebo were heterogeneous ($\chi^2 = 10.19$; $p<0.01$).

Phenobarbital versus placebo. Comparing phenobarbital *versus* placebo (Fig 1), the recurrence risk is lower in children treated with continuous phenobarbital (NNT 8; CI 95% 5 to 18; $z=3.46$ $p<0.05$). If we treat 8 children with phenobarbital, comparing to placebo group, one child would not have recurrence (OR for recurrence 0.54; 95% CI 0.38 to 0.76). In the phenobarbital group 24.5% (71/290) have recurrence and also 37.0% (114/308) of the placebo group. The results comparing the trials with phenobarbital and placebo were heterogeneous ($\chi^2 = 15.40$ $p<0.01$).

Intermittent diazepam or phenobarbital versus placebo. Comparing the prophylatic effect of phenobarbital or diazepam with placebo (Fig 1), we found that phenobarbital or diazepam reduces recurrence risk in febrile convulsion (NNT 12; 95 % CI 8 to 22; $\chi^2 = 25.76$ $p<0.02$), meaning that for each 12 treated children, one has no recurrence. OR for recurrence is 0.56 (95% CI 0.43 to 0.73; $z=-4.23$ $p<0.02$).

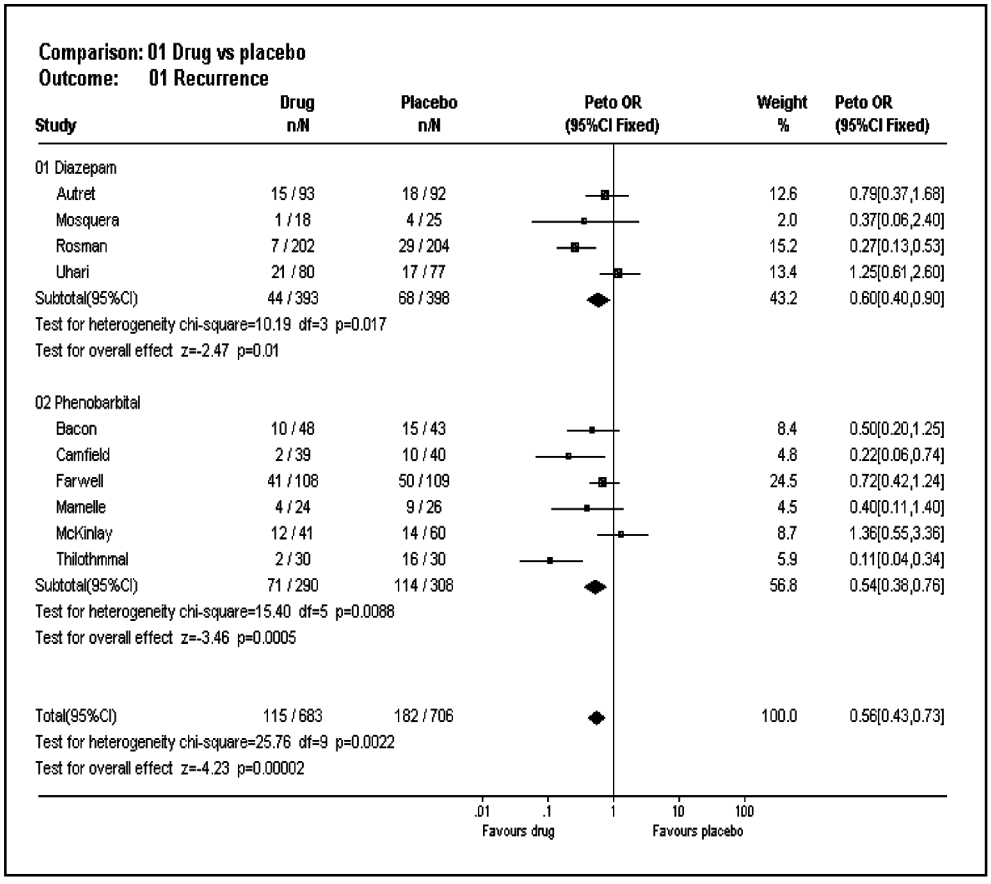

Fig 1. Odds Rartio (OR) and 95%CI in relation to number of recurrences with treatment Drug vs Placebo.

Table 1. Characteristics of the trials included in this review.

Author	Reference Number	Year	Randomization	Double-blind	Sample (N)	Exclusions	Loss N	Loss %
Knudsen	12	1978	C	-	195	0	39	20
Camfield	13	1980	B	A	79	0	12	15,2
Bacon	14	1981	B	A	207	0	69	33,3
Mamelle	15	1984	A	-	49	1	3	6,1
Mosquera	16	1987	A	-	43	0	4	9,3
Mckinlay	17	1989	B	-	101	0	13	12,9
Autret	18	1990	B	A	185	0	18	9,7
Farwell	6	1990	A	A	217	0	44	20.3
Rosman	2	1993	A	A	406	0	105	25,8
Thilothammal	4	1993	A	A	60	0	3	5
Uhari	19	1995	A	A	180	0	19	10.5

DISCUSSION

The most common treatment for febrile seizures has been the daily administration of phenobarbital or intermittent diazepam[8,12], a practice that has been questioned by many authors. Since seventies, several studies concerning treatment of febrile seizures have been published, but only 10 trials could be considered in our analysis, disclosing a lack of good stu-

Table 2. Trials using diazepam in relation to dose, treatment lasting, administration and follow-up.

Author	Dose (mg/Kg)	Frequency (Hours)	Duration of treatment (months)	Administration	Follow-up (months)
Rosman	0.33	8/8	23	OA	23
Mosquera	0.5	8/8	24	RA	24
Autret	0.2 –0.5	12/12	10.3	OA	10.3
Uhari	0.2 –0.65	8/8	24	RA	24

RA, rectal administration; AO, oral administration during the febrile episode

Table 3. Trials using phenobarbital in relation to dose, duration of treatment, administration and follow-up.

	Phenobarbital			
Author	Dose (mg/Kg/day)	Duration of treatment (months)	Administration	Follow-up (months)
Thilothammal	5	12	AO	12
McKinlay	5	3 - 6	AO	24
Farwell	4 – 5	24	AO	24
Mamelle	3 – 4	21	AO	36
Camfield	4 – 5	12	AO	12
Bacon	5	12	AO	12

AO, continuous oral administration

dies insuring a body of evidence to treat febrile seizures. Four studies (Table 2) comparing intermittent use of diazepam with placebo were found[2,16,18,19]. Autret[18], Mosquera[16] and Rosman[2] demonstrated the efficacy of diazepam in preventing febrile seizure in relation to placebo, but the results in Autret and Mosquera studies were not statistically significant. Rosman demonstrated that the diazepam treatment was more effective than placebo in his study, but more than 20% were lost in follow-up, which could modify the result significantly. Uhari's trial[19] showed no differences between the diazepam and placebo groups. The analysis of those four trials indicated that the risk for recurrent febrile seizures decreased with diazepam comparing to placebo, but the χ^2 test demonstrates that those studies are heterogeneous, which means that the results concerning to efficacy of randomized trials with intermittent diazepam therapy are controversial.

Among the studies (Table 3) comparing use of phenobarbital and placebo, in five ones[4,6,13-15] phenobarbital reduced the recurrence risk for febrile seizures. But in 3 studies[4,13-15], the relative reduced risk was not significant. Mckinlay[17] showed there was no difference in recurrence risk between phenobarbital and placebo.

The analysis of all studies (Table 4) in this meta-analytic review demonstrated that the treated group, either with intermittent diazepam or continuous phenobarbital, when compared with placebo group had a decreased recurrence risk of febrile seizure. The results were statistically significant, suggesting that the therapy is effective in preventing the febrile seizure recurrence. When we compared statistically the results, the χ^2 test showed heterogeneity of the trials, either due to methodological differences or clinical intrinsic differences of each study, and three possibilities arise to explain this heterogeneity: answers that do not agree with the trial quality, sample size and even clinical heterogeneity. However, in view of methodological differences of each study design, it is not possible to make a decision concerning the efficacy of diazepam or phenobarbital in preventing febrile seizures based on this systematic review and mostly on the meta-analytic study.

Clinical heterogeneity detected in those included

Table 4. Febrile seizure recurrence regarding to phenobarbital or diazepam compared to placebo.

Author	Reference Number	Year	N =children with Phenobarbital or Diazepam		
			Phenobarbital n/N	Diazepam n/N	Placebo n/N
Camfield	13	1980	2 / 39		10 / 40
Bacon	14	1981	10 / 48		15 / 43
Mamelle	15	1984	4 / 24		9 / 26
Mosquera	16	1987		1 / 18	4 / 25
Mckinlay	17	1989	12 / 41		14 / 60
Farwell	6	1990	41 / 108		50 / 109
Autret	18	1990		15 / 93	18 / 92
Rosman	2	1993		7/ 202	29 / 204
Thilothammal	4	1993	2 / 30		16 / 30
Uhari	19	1995		21 / 80	17 / 77

N, number of patients with recurrence; N, total number of patients in the sample.

trials was mostly related to clinical definition of febrile seizure patients allocated to treatment, age of patients (below or above 5 years), number of seizures, duration of seizures, co-morbidities, abnormal EEG, and doses of medication in the same drug option. We did not find a study that have calculated the number of patients necessary to allow statistical power for a scientific decision on the effectiveness of the treatment.

In conclusion the present systematic review and meta-analyses allow us to conclude that there is not a strong recommendation to treat febrile seizure either with continuous phenobarbital or with intermittent diazepam prophylaxis, because of the design and heterogeneity of the primary studies, but there is an evidence of potential benefit with the treatment of both drugs, although it is not possible to conclude which therapy is better, due to already mentioned heterogeneity of study design. The treatment decision should result from appropriate judgement and experience of the physician, and a standard trial with a large number of patients should be done to bring more information over this issues.

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