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Original Article

Prophylactic treatment of the recurrence of febrile convulsion by different drugs: a meta-analysis

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Abstract: Aims: The present study is to evaluate the effectiveness and safety of drugs in the prophylactic treatment of febrile convulsion (FC). Methods: Literatures published in any language were carefully searched in biological databases (PubMed, Embase, Medline, Cochrane Library, Chinese Biomedical Database, China National Knowledge Infrastructure, Chinese VIP Journal Database, Wanfang Database, and ClinicalTrials.gov) from the construction of the databases to 31 March 2016. Randomized controlled trials (RCTs) or quasi-RCTs were included in the analysis. Two investigators cross-checked the results of the literatures. Quality assessment of included RCTs was performed according to standards in Cochrane Handbook for Systematic Reviews of Interventions version 5.2. Meta-analysis was carried out using RevMan5.2 software. Results: A total of 17 literatures with 2,162 subjects were included in the meta-analysis. The overall quality of the included studies was low, except for 6 high-quality studies. Meta-analysis showed that the recurrence rate of FC in diazepam group was significantly lower than that in control group (OR = 0.28; 95% CI, 0.17-0.47, P < 0.00001). In addition, the recurrence rate of FC in phenobarbital group was significantly lower than that in control group (OR = 0.10; 95% CI, 0.05-0.18, P < 0.00001). However, the recurrence rate of FC in ibuprofen group was not significantly different from that in control group (OR = 0.77; 95% CI, 0.52-1.14, P = 0.2). Conclusions: The present study demonstrates that diazepam and phenobarbital significantly reduce the recurrence rate of FC. However, this result needs further studies in the future because of the low quality of the included studies.

Keywords: Febrile convulsion, recurrence, meta-analysis, diazepam, phenobarbital, ibuprofen

Introduction

Febrile convulsion (FC) is a common acute disease in pediatrics, with a prevalence rate of 3-5% in children. About 82% cases of FC are children aged six months to three years, and one third of the pediatric patients encounter recurrence [1]. If the pediatric patients cannot receive effective treatment and prevention, epilepsy or sequelae are likely to occur, and severely threaten the health of the children. The total probability of secondary epilepsy after febrile seizures is 2-6%, being 4 to 6 folds of that in healthy population [2]. There are two types of onset types, simple type and complex type. The incidence of secondary epilepsy after simple type of febrile seizures is 1.0-2.2%, being similar to that of healthy population. By contrast, the incidence of secondary epilepsy after complex type of febrile seizures is 4.1-6.0%, being significantly higher than that of simple type of febrile seizures [3]. It is reported that FC can cause a certain degree of brain damage, and patients with younger age of first onset, less mature nervous system, less perfect myelination, and higher sensitivity to hypoxia, ischemia, and acidosis are more likely to have the recurrence of FC [4, 5]. More recurrence times, more severe damages in hippocampal neurons and longer duration of convulsion can cause more severe brain injury. There are several ways to prevent FC [6], such as use of anti-convulsion drugs such as phenobarbital or sodium valproate, intermittent therapy and use of antifebrile. However, other researchers believe that the prognosis of FC children after recurrence is better [1], while whether drug treatment can really prevent recurrence still

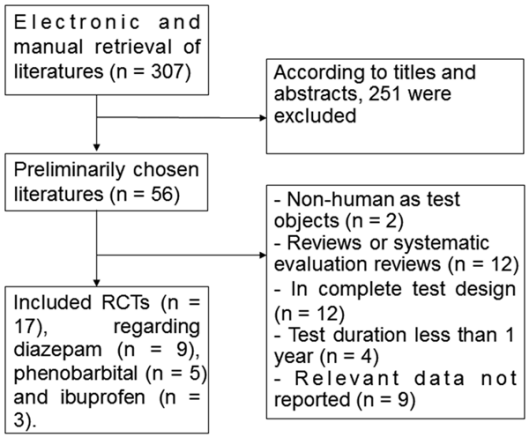

Figure 1. Flow chart of study selection process.

remains controversial. In the present study, we evaluate the effectiveness and safety of prophylactic drugs in the treatment of recurrent FC.

Materials and methods

Literature search

Literatures published in any language were carefully searched in biological databases (PubMed, Embase, Medline, Cochrane Library, Chinese Biomedical Database, China National Knowledge Infrastructure, Chinese VIP Journal Database, Wanfang Database, and ClinicalTrials.gov) from the construction of the databases to 31 March 2016. The search terms (both English and Chinese) included various combinations of "febrile seizure OR febrile convulsion", "recurrence", "prevention OR prophylaxis", and "medicine OR medication".

Inclusion and exclusion criteria

Randomized controlled trials (RCTs) or quasi-RCTs were included in the analysis, and the included literatures met the following criteria: i) The diagnosis of FC was in accordance with standards established by American Academy of Pediatrics in 2011 [2]; ii) age < 18 years; iii) experimental groups received preventive treatment by antiepileptic drugs or antipyretic analgesics, while control groups received placebo or nothing; iv) the included literatures were not guidelines and consensus, reviews, case reports; v) literatures with the most complete data from the same research institutions were chosen from a series of similar studies.

Outcome indices

Recurrence rate of FC after treatments with antiepileptic drugs or antipyretic analgesics was the main outcome index. The adverse reactions of these drugs were secondary outcome index.

Data extraction and quality assessment

Two investigators cross-checked the results of the literatures, and selected literatures strictly following the inclusion and exclusion criteria. In case of missing information, we contacted the authors by telephone or mail. The two investigators independently extracted relevant data, including i) general information such as titles, author names, publication date, and literature source; ii) research characteristics such as general conditions of subjects, baseline comparability of patients in each group, and intervention measures; iii) outcome indices. In case of any disagreement between the two investigators, the decision was made after thorough discussion or by a third investigator. Quality assessment of included RCTs was performed according to standards in Cochrane Handbook for Systematic Reviews of Interventions version 5.2 (random allocation method, allocation concealment, blind method for investigated subjects, therapeutic plan executor, and research outcome measurer, results data integrity, loss of follow-up, and withdrawal). If the number of losses of follow-up was more than 20% of the number of subjects included in the study, it is required to further analyze the reasons for the loss of follow-up, and to perform intention-to-treat analysis. In the meantime, JADAD rating scale [7] was used to score the quality of included literatures. Literatures with 0-2 points were of low quality, and those with 3-5 points were of high quality.

Statistical analysis

Meta-analysis was carried out using RevMan5.2 software (http://www.cochrane.org/) [8]. For count data, odds ratio (OR) was used to evaluate the efficacy; for measurement data, weighted mean difference (WMD) was used to evaluate the efficacy. The effect size was expressed as 95% confidence interval (CI). The heterogeneity among the results of included studies was examined using χ^2 test. If $P > 0.1$ and $I^2 < 50\%$, fixed effect model was used for analysis; If $P <$

Table 1. Basic characteristics of included studies

Literatures	Country	Study design	Tested drugs (mg/kg)	Control	No. of cases	Age (months)	Duration of treatment (days)	Follow-up duration (years)	JADAD score
Uhari 1995 [6]	Finland	RCT	Diazepam (0.2) Ibuprofen (5-8)	Placebo	180	6-60	1-5	2	3
Cai 1999 [7]	China	RCT	Diazepam (0.2-0.5)	Conventional antipyretic	77	6-60	2-5	2	1
Zhang 2001 [8]	China	RCT	Diazepam (0.2-0.5)	Conventional antipyretic	112	6-60	Until restoration to normal body temperature	1-5	1
Yun 2001 [9]	China	RCT	Diazepam (0.25)	Conventional antipyretic	42	6-60	Until restoration to normal body temperature	2	1
Verrotti 2004 [10]	Italian	RCT	Diazepam (0.35-0.5)	Placebo	110	6-60	3	2	3
Pavlidou 2006 [11]	Greece	RCT	Diazepam (0.35-0.5)	Placebo	139	6-36	3	2-5	4
Wang 2009 [12]	China	RCT	Diazepam (0.35-0.5)	Conventional antipyretic	160	4-96	1-5	2	1
Hennati 2013 [13]	Australia	RCT	Diazepam (0.2)	Placebo	186	6-60	Until restoration to normal body temperature	2	4
Wang 2013 [14]	China	RCT	Diazepam (0.2)	Conventional antipyretic	96	2-60	2-5	2	1
Yu 2003 [15]	China	RCT	Phenobarbital (4)	Conventional antipyretic	160	6-96	Until restoration to normal body temperature	2-5	1
Huang 2006 [16]	China	RCT	Phenobarbital (5)	Conventional antipyretic	65	6-60	Until restoration to normal body temperature	2	1
Mo 2006 [17]	China	RCT	Phenobarbital (3)	Conventional antipyretic	81	6-36	Until restoration to normal body temperature	1	1
Gao 2011 [18]	China	RCT	Phenobarbital (3-5)	Conventional antipyretic	105	6-36	Until restoration to normal body temperature	1-5	1
Long 2013 [19]	China	RCT	Phenobarbital (3-5)	Conventional antipyretic	80	6-72	Until restoration to normal body temperature	1-3	1
Van 1995 [20]	Holland	RCT	Ibuprofen (5)	Placebo	230	6-60	Until restoration to normal body temperature	2	3
Strengell 2009 [21]	Finland	RCT	Ibuprofen (10)	Placebo	231	6-60	Until restoration to normal body temperature	2	3
Zhang 2014 [22]	China	RCT	Ibuprofen (5-8)	Placebo	108	6-72	Until restoration to normal body temperature	2	1

Note: RCT, randomized controlled trial.

Table 2. Quality assessment of randomized controlled trials

Studies, year (reference)	Randomized	Allocation Concealment	Sequence Generation	Blinding of subjects	Selective reporting	Jadad score
Uhari 1995 [6]	Yes	Yes	Yes	Yes	No	3
Cai 1999 [7]	Yes	Unclear	Unclear	Yes	No	1
Zhang 2001 [8]	Yes	Unclear	Unclear	Yes	No	1
Yun 2001 [9]	Yes	Unclear	Unclear	Yes	No	1
Verrotti 2004 [10]	Yes	Yes	Unclear	Yes	No	3
Pavlidou 2006 [11]	Yes	Yes	Yes	Yes	No	4
Wang 2009 [12]	Yes	Unclear	Unclear	Yes	No	1
Hennati 2013 [13]	Yes	Yes	Yes	Yes	No	4
Wang 2013 [14]	Yes	Unclear	Unclear	Yes	No	1
Yu 2003 [15]	Yes	Unclear	Unclear	Yes	No	1
Huang 2006 [16]	Yes	Unclear	Unclear	Yes	No	1
Mo 2006 [17]	Yes	Unclear	Unclear	Yes	No	1
Gao 2011 [18]	Yes	Unclear	Unclear	Yes	No	1
Long 2013 [19]	Yes	Unclear	Unclear	Yes	No	1
Van 1995 [20]	Yes	Yes	Unclear	Yes	No	3
Strengell 2009 [21]	Yes	Yes	Yes	Yes	No	3
Zhang 2014 [22]	Yes	Unclear	Unclear	Yes	No	1

Note: Unclear-if allocation concealment or random sequence generation or outcome assessment is not reported.

0.1 and I^2 > 50%, the source of heterogeneity was analyzed, and then whether random effect model could be used was evaluated. If there was significant clinical heterogeneity among the studies, only descriptive analysis was performed.

Results

Characteristics of the included studies

A total of 307 literatures were acquired by searching. By reviewing titles and abstracts, 251 literatures were excluded and 56 literatures regarding preventive treatment of FC by drugs were preliminarily chosen. According to the inclusion and exclusion criteria, 17 literatures [9-25] with a total of 2,162 subjects were finally included in the meta-analysis (**Figure 1**). Of note, 5 literatures were published in English, while the other 12 literatures were published in Chinese. All of the included subjects were children aged between 6 and 60 months. Diazepam was investigated in 9 RCTs [9-17], phenobarbital was studied in 5 RCTs [18-22], and ibuprofen was studied in 4 RCTs [9, 23-25]. In most studies, the course of treatment was not definite, and the treatment was continued until the restoration of the normal body temperature. The follow-up period was 1 to 5 years (**Table 1**).

Quality assessment of the included studies

To assess the quality of the included studies, JADAD scoring system was used. The overall quality of the included studies was low, except for 6 high-quality studies [9, 13, 14, 16, 23, 24] (**Table 2**).

Analysis of FC recurrence rates

Among the 17 included literatures, 9 literatures [9-17] reported the recurrence rates of FC after treatment with diazepam. The heterogeneity among studies was great (I^2 = 58%), so random effects model was used. Meta-analysis showed that the recurrence rate of FC in diazepam group was significantly lower than that in control group (OR = 0.28; 95% CI, 0.17-0.47, P < 0.00001) (**Figure 2**). In addition, 5 literatures [18-22] reported the recurrence rates of FC after treatment with phenobarbital. The heterogeneity among studies was small (I^2 = 8%), so fixed effects model was employed. Meta-analysis showed that the recurrence rate of FC in phenobarbital group was significantly lower than that in control group (OR = 0.10; 95% CI, 0.05-0.18, P < 0.00001) (**Figure 3**). Moreover, 4 literatures [9, 23-25] reported the recurrence rates of FC after treatment with ibuprofen. There was no heterogeneity among included studies (I^2 = 0), so fixed effects model was

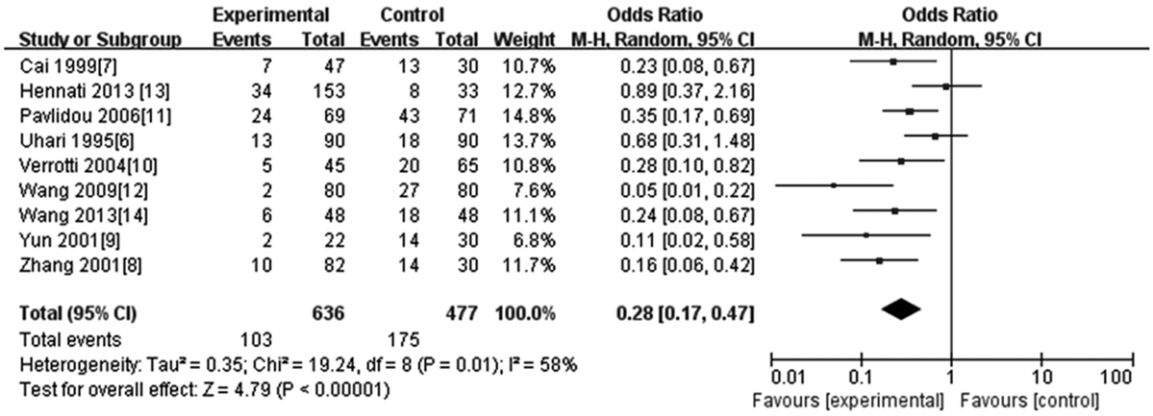

Figure 2. Meta-analysis of recurrence rate of FC after treatment with diazepam.

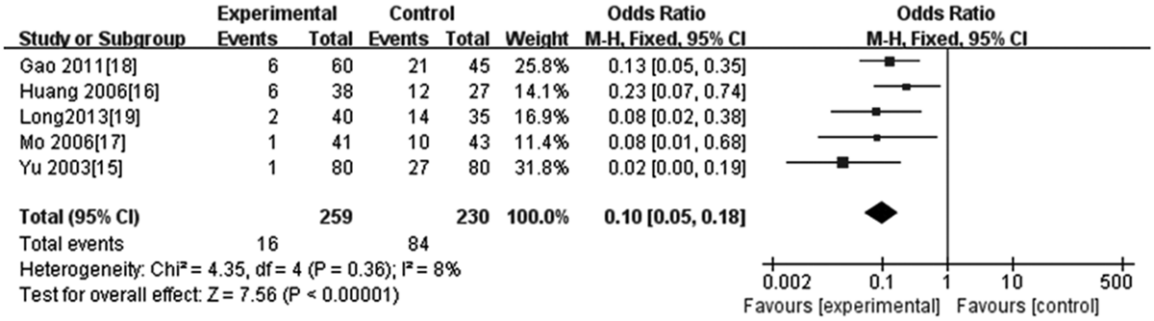

Figure 3. Meta-analysis of recurrence rate of FC after treatment with phenobarbital.

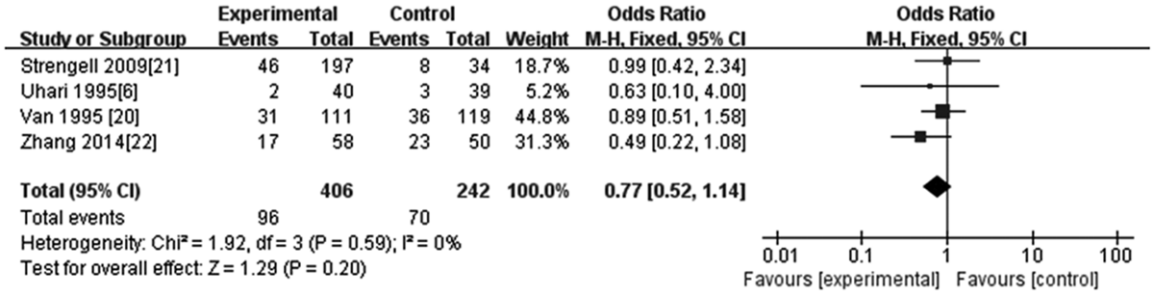

Figure 4. Meta-analysis of recurrence rate of FC after treatment with ibuprofen.

employed. Meta-analysis showed that the recurrence rate of FC in ibuprofen group was not significantly different from that in control group (OR = 0.77; 95% CI, 0.52-1.14, P = 0.2) (**Figure 4**). These results suggest that diazepam and phenobarbital, but not ibuprofen, are able to reduce the recurrence of FC.

Analysis of safety

Regarding the safety of the diazepam, 3 literatures [11, 15, 17] did not report adverse event data during treatment, 2 literatures [13, 16] reported drowsiness (14%) and irritability (39%) during treatment, 3 cases quitted studies due to adverse events [16], and 2 literatures [12, 13] reported mild and short dystaxia (31% and 10%, respectively) that was alleviated after withdrawal or reduction of the drug. Among the 5 literatures regarding phenobarbital, only 1 literature [21] reported 4 cases with mild drowsiness, which disappeared after withdrawal of the drug. In addition, no relevant adverse reac-

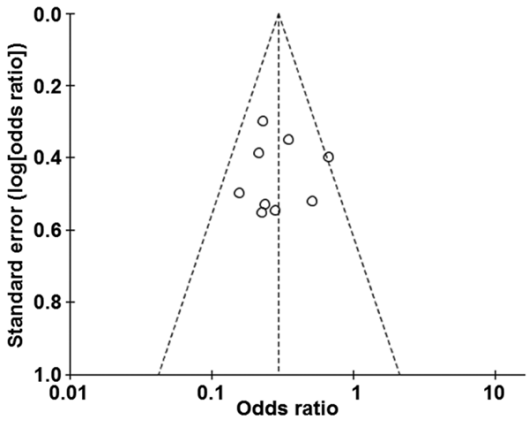

Figure 5. Assessment of publication bias. Begg's funnel plot was produced using the recurrence rate after treatment with diazepam as the outcome indictor.

tions were reported in the three studies on ibuprofen.

Assessment of publication bias

To test whether the included articles had publication bias, Begg's funnel plot was produced using the recurrence rate after treatment with diazepam as the outcome indictor. The data showed that the funnel plot was symmetrical (**Figure 5**). The result suggests that the included articles have low risk for publication bias.

Discussion

The occurrence of FC is mainly related to the simple structure of brain cells in infants, incomplete functional differentiation and axonal branching, incomplete myelin sheath formation, activity of chemical composition enzymes of brain tissue, and excitatory and inhibitory transmitters [26]. Currently, there is controversy about the efficacy of prophylactic drug therapy on recurrent FC. Offringa et al. [27] and Masuko et al. [28] show that intermittent oral or rectal administrations of diazepam, phenobarbital, phenytoin sodium, sodium valproate, vitamin B6, ibuprofen, diclofenac sodium and paracetamol have no clinical significance on the prevention of recurrent FC. By contrast, the effect of intermittent oral urbanyl is better, but this is reported in only one study [29] and needs more clinical trials to validate.

The present study demonstrates that oral intake of diazepam and phenobarbital significantly reduces the recurrence rate of FC, but ibuprofen has no therapeutic effect. These findings are inconsistent with the studies by Offringa et al. [27] and Masuko et al. [28], probably because the latter studies have included smaller number of cases and the included subjects are mainly European and American caucasians. Of note, only a few literatures included in the present study have reported safety of the drugs. FC occurence has a property of self-confinement, and children with recurrent FC are able to obtain relatively good prognosis [30]. Because anti-epileptic drugs and antipyretics have high rates of adverse reactions, it is not beneficial to use drugs on FC children. Abused use of drugs on FC children not only increases the extra mental and economic burdens, but also causes physical damage and pain in the children. Therefore, more clinical trials are still required before recommending these drugs in the prevension of recurrent FC.

There are still some limitations in the present study. Firstly, the general conditions of subjects should have been clearly defined, such as gender, age, disease history, medication adherence, and family economy. Secondly, blank or placebo-controlled trials should be included, and the implementation of random and blind methods should be described in details. Thirdly, the effects of dosage, dosage form, administration modes, and intervention time and duration should be analyzed regarding intervention measures. Fourth, immediate, short-term and long-term follow-ups should be recorded separately, and the number of losses of follow-ups should be recorded and analyzed. Lastly, heterogeneity evaluation should be performed, and data should be analyzed in sub-groups with different factors. In conclusion, the present study demonstrates that diazepam and phenobarbital significantly reduce the recurrence rate of FC. However, the long-term effects and safety of these drugs should still be further studied because of the low quality of the included studies. Therefore, it should be cautious to use these drugs in the prevention of FC in children.

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Disclosure of conflict of interest

None.

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References

[1] Pavlidou E, Hagel C and Panteliadis C. Febrile seizures: recent developments and unanswered questions. Childs Nerv Syst 2013; 29: 2011-2017.

[2] Patterson JL, Carapetian SA, Hageman JR and Kelley KR. Febrile seizures. Pediatr Ann 2013; 42: 249-254.

[3] Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 2008; 121: 1281-1286.

[4] Dube C, Chen K, Eghbal-Ahmadi M, Brunson K, Soltesz I and Baram TZ. Prolonged febrile seizures in the immature rat model enhance hippocampal excitability long term. Ann Neurol 2000; 47: 336-344.

[5] Lado FA, Laureta EC and Moshe SL. Seizure-induced hippocampal damage in the mature and immature brain. Epileptic Disord 2002; 4: 83-97.

[6] Xu J. Several problems in the diagnosis and treatment of febrile seizures. Pediatr Emerg Med 2000; 7: 51.

[7] Jadad AR, Cook DJ and Browman GP. A guide to interpreting discordant systematic reviews. CMAJ 1997; 156: 1411-1416.

[8] Higgins J and Green S. Cochrane handbook for systematic reviews of interventions The Cochrane Collaboration, 2011.

[9] Uhari M, Rantala H, Vainionpaa L and Kurttila R. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. J Pediatr 1995; 126: 991-995.

[10] Cai X, Lu D and Chen R. A prospective study on oral diazepam to prevent recurrence of febrile convulsion in children. Chin J Prac Pediatr 1999.

[11] Zhang S and Shi Y. Effect of short course of oral diazepam on prevention of recurrence of febrile convulsion. J Appl Clin Pediatr 2001; 16: 106-107.

[12] Yun X. Preventive treatment of recurrence of febrile convulsion in children with low dose diazepam. Inn Mongol Med J 2001; 33: 164.

[13] Verrotti A, Latini G, di Corcia G, Giannuzzi R, Salladini C, Trotta D and Chiarelli F. Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. Eur J Paediatr Neurol 2004; 8: 131-134.

[14] Pavlidou E, Tzitiridou M and Panteliadis C. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: long-term prospective controlled study. J Child Neurol 2006; 21: 1036-1040.

[15] Wang R. Diazepam to prevent recurrence of febrile convulsion in children: analysis of 80 cases. Chuan Bei Yi Xue Yuan Xue Bao 2009; 2: 156-157.

[16] Hemmati M. Survey the effect of oral diazepam in prevention of febrile seizure. Intensive Care Med 2013; 39: 103.

[17] Wang G and Li K. Analysis of the efficacy of oral diazepam to prevent recurrence of febrile convulsion. Guide of China Medicine 2013; 12: 585-586.

[18] Yu Y. Phenobarbital for the prevention of febrile seizure recurrence: analysis of 60 cases. J Pediatr Phar 2003; 3: 24-25.

[19] Huang X and Li X. Phenobarbital for the prevention of recurrence of febrile seizures in children. Clin Med (Lond) 2007; 5: 54-55.

[20] Mo C and Lan G. The prevention of recurrence of phenobarbital on febrile convulsion. J Clin and Exp Med 2006; 7: 922.

[21] Gao Q. Analysis of curative effect of phenobarbital in the prevention of recurrence in children with complicated febrile convulsion. Shan Xi Zhi Gong Yi Xue Yuan Xue Bao 2011; 2: 25-26.

[22] Long T. Analysis of therapeutic effect of phenobarbital for the prevention of recurrence of febrile convulsion. Contemp Med 2013; 29: 139-140.

[23] van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, Habbema JD and Moll HA. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics 1998; 102: E51.

[24] Strengell T, Uhari M, Tarkka R, Uusimaa J, Alen R, Lautala P and Rantala H. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Arch Pediatr Adolesc Med 2009; 163: 799-804.

[25] Zhang F and Meng W. Efficacy observation of retention enema with diazepam and ibuprofen in prevention of febrile convulsion in children. Chin J Healthy Birth & Child Care 2014; 4: 220-222.

[26] Chung S. Febrile seizures. Korean J Pediatr 2014; 57: 384-395.
[27] Offringa M and Newton R. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 2012; 4: Cd003031.
[28] Masuko AH, Castro AA, Santos GR, Atallah AN, do Prado LB, de Carvalho LB and do Prado GF. Intermittent diazepam and continuous phenobarbital to treat recurrence of febrile seizures: a systematic review with meta-analysis. Arq Neuropsiquiatr 2003; 61: 897-901.
[29] Al Faleh K and Al-Omran M. Reporting and methodologic quality of Cochrane neonatal review group systematic reviews. BMC Pediatr 2009; 9: 38.
[30] Erkek N, Senel S, Sahin M, Ozgur O and Karacan C. Parents' perspectives to childhood fever: comparison of culturally diverse populations. J Paediatr Child Health 2010; 46: 583-587.