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Editorial

Febrile seizures: the role of intermittent prophylaxis

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Febrile seizure (FS) is the most common seizure type of the childhood and known as a benign condition which usually does not require any acute intervention or long-term therapy [1,2]. "No treatment" approach for febrile seizures was universally accepted and recommended between the periods 1930 and 1950. However, later, between 1960 and 1980, with the emerging reports in neurosurgical literature describing the association between the prolonged febrile seizure and temporal lobe epilepsy led the implementation of continuous prophylaxis with phenobarbital without carefully review of the results from clinical trials. It was aimed to prevent the temporal lobe epilepsy secondary to mesial temporal sclerosis with continuous prophylaxis. The relationship between the FS and temporal lobe epilepsy still has remained controversial. Retrospective and prospective studies showed supporting evidence as well as contradictory results [3]. It is widely recognized now that the cumulative evidence from randomized controlled studies has revealed that febrile seizures mostly are self-limited benign conditions with good outcome [4–7]. Most children with FS, never developed epilepsy, but 2–3% may develop unprovoked recurrent seizures by 7 years of age with slightly higher incidence than the one in normal population [8]. Three independent risk factors were identified for occurrence of later epilepsy: history of idiopathic epilepsy in the family members, abnormal neurological and developmental status and complex FS. The children with 2 or 3 risk factors are considered as high-risk group for epilepsy, with a rate of 10% by age of 7 years [8,9].

Neither intermittent nor continuous treatment with antiepileptic medications does reduce the risk for unprovoked seizures or epilepsy, but reduces the incidence of recurrent FS [10–15]. Continuous prophylaxis with phenobarbital and other antiepileptic drugs such as valproic acid, carbamazepine and phenytoin were studied for short-term outcome [16–18]. Particularly, continuous prophylaxis resulted in serious side effects on cognition and behavior. Farwell et al. [19] reported that phenobarbital decreased the total intelligent quotients (IQs) 7.03 points in the treatment group compared with control group at the end of the 2 year follow-up. Sixth months after the discontinuation of phenobarbital, the mean IQ score was still 5.2 points lower in the group assigned to phenobarbital [19]. Intermittent prophylaxis with antiepileptic medications such as phenobarbital or valproic acid did not reveal any benefit, but potential risk for side effects, particularly with phenobarbital [20]. On the other hand, intermittent use of benzodiazepines, especially diazepam prophylaxis presented promising results. The intermittent prophylaxis can be administered via oral, rectal or sublingual route. At least 13 uncontrolled studies have documented the

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efficacy of diazepam via either oral or rectal administration. Knudsen [21] presented a short term prophylaxis with diazepam in a clinically controlled trial with 289 children following a first FS. These children were randomized into 2 groups as, a group received diazepam at the fever onset and the group received diazepam in solution at the seizure onset. The intermittent prophylaxis at the onset of fever showed that the 18-months cumulative recurrence rate reduced from 38 to 12% with the intermittent diazepam prophylaxis compared the group received the treatment at the seizure onset [21]. The number of prolonged recurrences decreased from 5.0 to 0.7%. A Dannish trial compared intermittent treatment with diazepam suppositories at times of fever in 83 children, and chronic phenobarbital prophylaxis in 73 children. The 12-month recurrence rates were found 15 and 16%, which was below the spontaneous recurrence rate [17]. There are only three placebo randomized controlled studies analyzed the efficacy of intermittent diazepam prophylaxis [22–24]. However the meta-analysis of these studies failed to show a benefit of intermittent prophylaxis with diazepam [25]. The study from the United States by Rosman et al. [22] showed that the intermittent oral administration of diazepam at the onset of fever was effective for decreasing the recurrent FS when it is given during the course of febrile illness. However, two other studies had methodological problems, and presented no significant seizure control. Autret et al. [24] from France found the lack of efficacy but also poor compliance rate. Uhari et al. [23] in a placebo-controlled double blind study demonstrated that the intermittent use of acetaminophen or diazepam has no effect on recurrence of FS. However, the dose of diazepam used in that study was 0.2 mg/kg, lower that the dose universally recommended. Therefore, these results should be carefully reviewed and interpreted with caution.

When should we consider the intermittent prophylaxis for FS? It was shown that the selection of the children for intermittent prophylaxis is important to achieve the goal to reduce the recurrent FS. Several predictors were identified for recurrent FS. The young age of onset is found to be strongest predictor for recurrent FS followed by family history of FS as well as day nursery attendance [26,27]. The occurrence of complex FS such as prolonged FS, seizures with focal features or recurrent seizures within a 24 hour period during the same febrile illness remain as a weak predictor. Presence of more risk factors brings more chance for recurrent FS. The children with a single risk factor fall in the low risk group, whereas two risk factor in intermediate and three and more risk factors in high risk group. Intermittent prophylaxis did not bring a remarkable benefit for the recurrent FS to the low or intermediate risk group, but remarkably to the high-risk group [21]. The children with multiple risk factors for recurrent FS seem to have lower recurrence rate than children experienced FS at younger age [21,28].

Not only diazepam, but also the other benzodiazepines were studied for the intermittent prophylaxis of FS. Nitrazepam, clonazepam and midazolam were found to be efficacious for prevention of recurrent FS [29,30]. In this issue of Journal of Pediatric Neurology, Bajaj et al. [31] examined the efficacy of the intermittent prophylaxis with clobazam for FS in a double blind, placebo controlled study. Their result demonstrated that the recurrence rate is significantly lower in the clobazam group with fewer side effects. The authors did not mention about the compliance factor in their study, but a 6 month follow-up period may have eliminated this problem which was an obstacle in the other earlier studies. Cost effectiveness and availability of clobazam might be a potential problem in developing countries, especially in comparison with diazepam.

In summary, FS remain as a benign conditions as reported in early 20th century. The continuous prophylaxis with phenobarbital is no longer recommended because of the serious long-term side effects. Studies documented that prophylaxis did not provide better efficacy than acute treatment of the seizures in regards of cognitive functions, developmental outcome and occurrence of epilepsy in the future [32–36]. Therefore, prophylaxis should be reserved for the group of children with history of prolonged FS or febrile status epilepticus, presence of multiple risk factors for recurrences, and a strong parental anxiety and pressure for the treatment. Benefit should outweigh the risk of prophylactic treatment if needs to be offered. Intermittent prophylaxis with benzodiazepines is useful and applicable for parents and caregivers in home setting, which may eliminate the risk for unnecessary emergency room visit as well as possibility of prolonged FS or febrile status epilepticus. However the appropriate dosing and compliance would be essential to achieve the goal from intermittent prophylaxis.

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