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Original Article

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**Efficacy and Safety of Continuous Subcutaneous Insulin Infusion vs. Multiple Daily Injections on Type 1 Diabetes Children Aged  $\leq$  18 Years Old, a Meta-Analysis with Randomized Control Trials**

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**What is already known on this topic?**

A previous meta-analysis on children with type 1 diabetes also indicated the advantages of CSII in blood glucose control. However, bias caused by age may exist.

**What this study adds?**

The glucose control can be improved by CSII compared with MDI in children with type 1 diabetes aged  $\leq$  18 years old. The significantly reduced insulin requirement can be obtained after long term CSII treatment (12 months), compared with MDI. Age, treatment duration and study design are factors impacting the efficacy of CSII and MDI in children with type 1 diabetes.

**Abstract**

**Objective:** This meta-analysis was performed to evaluate efficacy and safety of Continuous subcutaneous insulin infusion (CSII) vs. Multiple daily injections (MDI) in children with type 1 diabetes.

**Methods:** A literature search was conducted on databases including PubMed and Embase up to June 2017. The pooled weighted mean difference (WMD) or risk ratio (RR) as well as 95% confidence intervals (CIs) were calculated by Revman 5.3.

**Results:** 8 studies involving 310 children with type 1 diabetes were included. Results showed that HbA1c (%) was significantly lower ( $P = 0.007$ ) after treating by CSII compared with MDI in children with type 1 diabetes. In addition, there was no significant difference between groups in HbA1c (%) change, total daily insulin doses per day, change of total daily insulin doses per day and incidence of ketoacidosis and severe

hypoglycemia. However, subgroup analyses indicated that age, treatment duration and study design are factors impacting the efficacy of CSII and MDI in children with type 1 diabetes.

**Conclusions:** In conclusion, CSII is associated with lower HbA1C levels in children with type 1 diabetes but may have no effect on insulin requirement and reducing incidence of ketoacidosis and severe hypoglycemia.

**Keywords:** Continuous subcutaneous insulin infusion, Multiple daily injections, children, type 1 diabetes, meta-analysis.

## **Introduction**

Type 1 diabetes is diabetes caused by the immune system attacking and destroying the beta cells in the pancreas that produce insulin, and commonly occurred in childhood with still increasing incidence in recent years [1]. Multiple daily injection (MDI) treatment is the most widely used method of insulin administration for treating diabetes, which requires at least 3 or more injections a day. For reducing the complications and improving blood glucose control, continuous subcutaneous insulin infusion (CSII) has been used as a popular option for diabetes management yearly, especially in preschool-aged children [2, 3]. Recently, many meta-analyses have been performed to compare MDI and CSII in adult patients with type 1 diabetes [4, 5]. In these studies, CSII indicated many advantages including improvement of blood glucose control, reduction of daily insulin requirement, and increase of treatment satisfaction. In addition, a previous meta-analysis [6] on children with type 1 diabetes also indicated the advantages of CSII in blood glucose control. However, a study investigating patients aged larger than 18 years [7] was included in that meta-analysis, so bias caused by age may impact the results of that meta-analysis. Thus, it is necessary to compare the efficacy and safety of CSII and MDI with studies only on children aged  $\leq 18$  years old. In addition, we also investigated the influence of treatment duration, age and study design on efficacy comparison of CSII and MDI.

## **Materials and methods**

The methods used for this meta-analysis and generation of inclusion criteria were based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations. Approval by a research ethics committee to conduct this meta-analysis was not required.

## **Literature search strategy**

Databases including PubMed and Embase were used for literature search up to June 2017, using the following keywords: ((insulin infusion) OR (insulin pump)) AND (children) AND ((diabetes) OR (diabetic)). In addition, the references of relevant reviews were searched for additional studies.

## **Inclusion and exclusion criteria**

The following criteria should be met for all included studies: (1) the study type was randomized study; (2) subjects were children with type 1 diabetes aged  $\leq 18$  years old; (3) the CSII was used for glucose control (experimental group) compared with conventional MDI (control group); (4) clinical outcomes included at least one of the followings, such as HbA1c (%), insulin dose and some adverse events.

The studies should be excluded if they were (1) duplicated publications, or (2) reviews, letters, or comments.

## **Data extraction and quality assessment**

The following data were recorded in a predesigned form: first author name, country, year, enrolled time,

duration of diabetes, treatment duration, sample size, age, sex, treatment target, and outcomes. The data extraction was performed independently by two investigators. The quality of included studies was assessed by the Cochrane Collaboration's tool for assessing risk of bias as shown in the previous studies [8]. For data extraction and quality assessment, differences were resolved by discussion to ensure consistency of evaluation.

### **Statistical analysis**

The Revman 5.3 software was used to perform this meta-analysis. The I-squared and Cochran Q tests were used to assess the heterogeneity using  $P < 0.1$  or  $I^2 > 50\%$  indicating significant heterogeneity. An appropriately statistical model (fixed effect model or random effects model) was applied to pool the weighted mean difference (WMD) or risk ratio (RR) as well as the corresponding 95% confidence intervals (CIs), based on the results of heterogeneity test. The subgroup analysis was performed based on the age, treatment duration and study type. Publication bias was assessed using the Egger's and Begg's Test. For all these analyses,  $p < 0.05$  indicated statistical significance.

### **Results**

#### **Characteristics of included studies**

After initial literature search, a total of 312 articles (PubMed:  $n = 175$ , Embase:  $n = 137$ ) were identified. After excluding duplicates, 88 potentially relevant articles were remained. Of these, 56 articles were excluded including 15 obvious irrelevant studies, 25 non-RCTs and 16 reviews. Then the remaining 32 articles were assessed by reading the full-text. Among them, 26 articles were excluded (10 were non-RCTs, 4 articles did not report available data, 6 articles did not use the insulin injection, and 4 studies enrolled some participants aged over 18 years old). Finally, 8 studies [9-16] were included for performing this study (Figure 1).

The characteristics of included studies were shown in Table 1. A total of 310 children with type 1 diabetes in these included studies were included and reanalyzed in this meta-analysis. The duration of diabetes was all longer than one year. The publication year ranged from 2003 to 2014. There were 6 randomized control trials and 2 randomized crossover trials. The treatment durations ranged from 3.5 to 24 months. The bias risk assessment was shown in Table 2. No study applied or reported the blind method. Performance bias was only avoided by crossover design in the studies of Naomi Weintrob 2004 and 2003 [12, 13].

#### **Meta-analysis**

Among these 8 included studies, all of them considered the glucose control outcomes. As shown in Figure 2A, the HbA1c (%) was significantly lower (WMD = -0.25, 95% CI = -0.43 to -0.07,  $P = 0.007$ ) after treating by CSII compared with MDI in children with type 1 diabetes. However, the significant difference disappeared in the subgroup analyses (Table 3) by studies with crossover design ( $P = 0.53$ ) or prepubertal school aged and pubertal patients ( $P = 0.05$ ). Moreover, no significant difference was found in mean change of HbA1c (%) (mean difference from baseline to end of study) between the children treated with CSII and MDI in overall analysis (WMD = -0.02, 95% CI = -0.18 to 0.15,  $P = 0.84$ , Figure 2B) and subgroup analyses ( $P > 0.05$ , Table 3).

As shown in Figure 2C, the total daily insulin doses per day was similar in diabetic children after treating by CSII and MDI (WMD = -0.14, 95% CI = -0.34 to 0.06,  $P = 0.16$ ). The mean change of total daily insulin doses per day from the baseline to the end of study (mean difference from baseline to end of study) was

also similar between CSII and MDI groups (WMD = -0.11, 95% CI = -0.25 to 0.03, P = 0.13, Figure 2D). In the subgroup analyses, the results indicated that children with type 1 diabetes needed significantly less daily insulin doses per day after 12 months CSII treatment compared with MDI (WMD = -0.21, 95% CI = -0.36 to -0.05, P = 0.009, Table 3).

For the adverse events, there was no significant difference in the incidences of ketoacidosis (RR = 2.22, 95% CI = 0.75 - 6.59, P = 0.15, Figure 2E) and severe hypoglycemia (RR = 0.77, 95% CI = 0.45 - 1.32, P = 0.34, Figure 2F) between the children treated with CSII and MDI. No inconsistent results for analysis of incidence of severe hypoglycemia were found in subgroup analysis (P > 0.05, Table 3).

### **Heterogeneity results**

In overall analyses, significant heterogeneity (P < 0.1 or I<sup>2</sup> > 50%) among studies was found in analyses for HbA1c (%), total daily insulin doses per day, and change of total daily insulin doses per day, so the randomized effects model was applied to pool the data. Fixed effect model was used for other analyses (Figure 2). However, these significant heterogeneities were still absent (P > 0.1 or I<sup>2</sup> = 0%, Table 3) among studies in some subgroup analyses for HbA1c (%) (treatment duration, 3/3.5 months; study design, crossover design; age, prepubertal school aged and pubertal patients) and change of total daily insulin doses per day (treatment duration, 6 months). Thus, beside age, treatment duration and study design, there were other sources of heterogeneity.

### **Publication bias**

No significant publication bias was found by Egger's and Begg's Test in this study (P > 0.05).

### **Discussion**

In this study, significantly lower HbA1c (%) was indicated in CSII group compared with MDI group. Moreover, subgroup analysis showed significant difference between groups after both 3/3.5 months and 6 months treatment. However, many retrospectively or prospectively observational studies were published and reported the long term outcomes on HbA1c in type 1 diabetes children [17, 18], indicating CSII may had significant better efficacy on glucose control after long term treatment. More studies should be performed to investigate the efficacy difference between long-term and short-term treatment. Subgroup analysis also showed that study design may be a factor affecting the results based on the subgroup analysis by study design for HbA1c (%). Lack of effect in RCOT suggest training in diabetes management may be main cause explaining CSII effects. In addition, the mean change of HbA1c (%) was similar among groups. The different baseline level or lack of enough studies may be the factors resulting the similar results between CSII and MDI groups. Furthermore, the effect of CSII on HbA1c (%) may be related to higher diabetic education level of children with Diabetes and their families. The family or children treated by CSII may receive more diabetic education due to more opportunity to contact new treatment information and good economic incomes. More studies should be performed to investigate the impact of diabetic education level on CSII or MDI treatment efficacy.

However, based on the results of subgroup analyses, the advantage (reducing HbA1c (%)) of CSII compared with MDI was absent in prepubertal school aged and pubertal patients in this study (P = 0.05).

Thus, age may be a factor affecting the efficacy of CSII and MDI treatment for type 1 diabetes. The mainly pathogenesis of type 1 diabetes is immune system related cell injury in the pancreas. More and more strong immune system by the increasing of age may be a mechanism of different efficacy by CSII and MDI between pre-school aged children and prepubertal school aged and pubertal patients. Significant

heterogeneity ( $I^2 = 70\%$ ,  $P = 0.02$ ) existed among the included studies on prepubertal school aged and pubertal patients. Thus, the results may be instable. More studies should be performed to confirm the impact of age on efficacy of CSII and MDI.

In addition, the insulin requirement could be significantly reduced after long-term (12 months) CSII treatment compared with MDI, but not after short-term treatment (6 months), which is inconsistent with the previous meta-analysis [11]. This previous meta-analysis included a study on type 1 diabetes patients aged 8-21 years old [7]. The adult patients (aged larger than 18 years old) with type 1 diabetes may result in bias risk affecting the results on children. Thus, we only included studies with children aged  $\leq 18$  years old in this meta-analysis to further confirm the comparison results between CSII and MDI. Moreover, we included more studies in this meta-analysis, such as Opiari-Arrigan L 2007, Skogsberg L 2008 and Fawzia Elsayed Abusaad 2014 [1, 10, 16]. In addition, compared with that previous meta-analysis, we performed the subgroup analyses by study design. The heterogeneity changes and inconsistent results between subgroup analyses and overall analyses indicated that age, study design and treatment duration may be sources of heterogeneity and factors impacting the efficacy of CSII and MDI in children with type 1 diabetes.

In addition, no significantly different incidence of complications (ketoacidosis and severe hypoglycemia) were found in this meta-analysis. However, some previous observational studies indicated that the CSII could significantly reduce the incidence of severe hypoglycemic episodes compared with MDI after long term treatment (5 years) [19]. Thus, more study with longer follow up should be performed to further compare the complications after CSII and MDI in children with type 1 diabetes and explore the factors influencing the safety of CSII and MDI in children with type 1 diabetes.

#### **Study limitations**

Some disadvantages should be noted. Firstly, the number of included studies and sample size were small. Secondly, the significant heterogeneity was found in this study. Although the subgroup analyses were performed, the significant heterogeneity still existed in some subgroup analyses. Except study design, age and treatment duration, some other confounding factors (such as sex, duration of diabetes, country and treatment target) may also be the sources of heterogeneity. As the increase of duration of diabetes, there is more and more high risk of "burn-out" and noncompliance of patients, which will affect the efficacy of treatment for glycemic control. However, the data for duration of diabetes is inadequate in these included studies to perform the subgroup analyses in this meta-analysis. Therefore, this factor (duration of diabetes) will be investigated in further studies. Thirdly, except HbA1c (%), duration of blood glucose value at the target range is also the key index evaluating the efficacy of blood glucose control. However, no enough data to perform subgroup analysis in the meta-analysis. In addition, more RCTs should be performed with larger sample size in future.

#### **Conclusions**

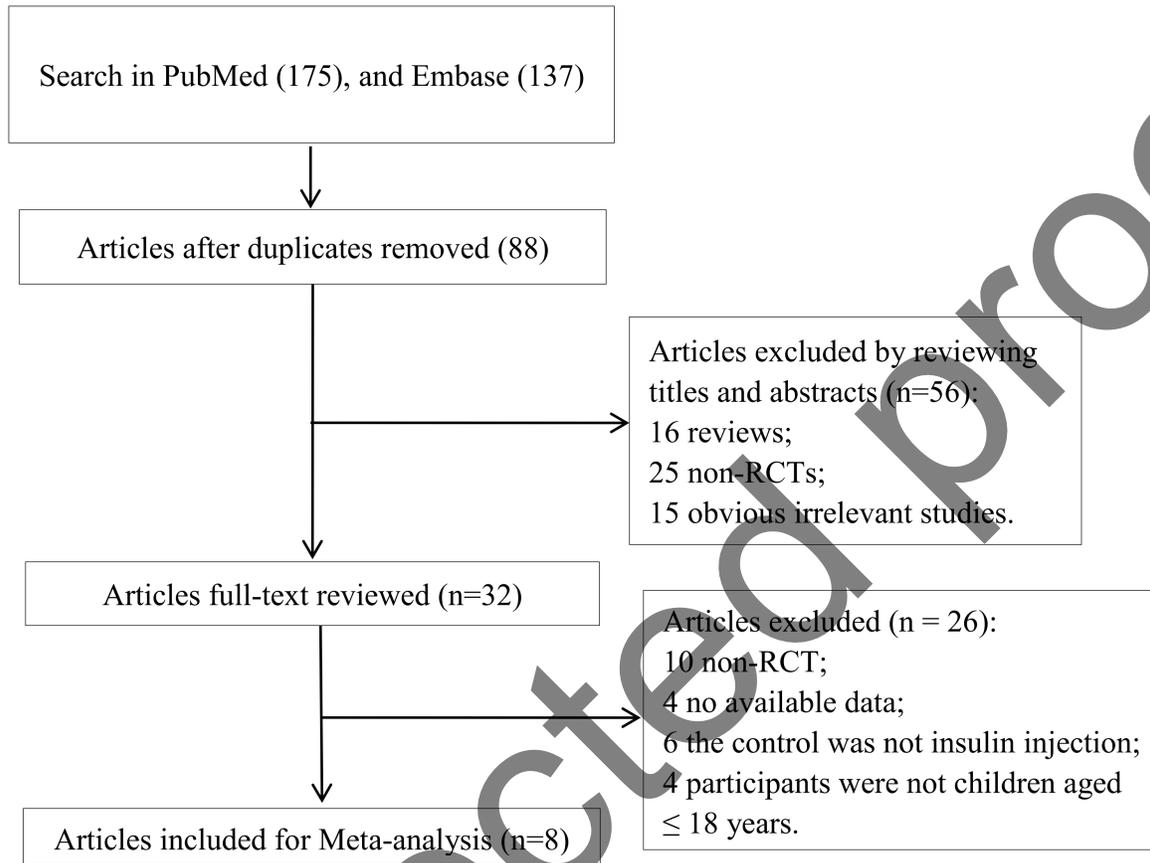
In conclusion, CSII is associated with lower HbA1C levels in children with type 1 diabetes but may have no effect on insulin requirement and reducing incidence of ketoacidosis and severe hypoglycemia. Age, treatment duration and study design may be the factors influencing the comparison results. Diabetic education level may be one of the important factor influencing the treatment efficacy. More studies should be performed to investigate the impact of diabetic education level on CSII or MDI treatment efficacy.

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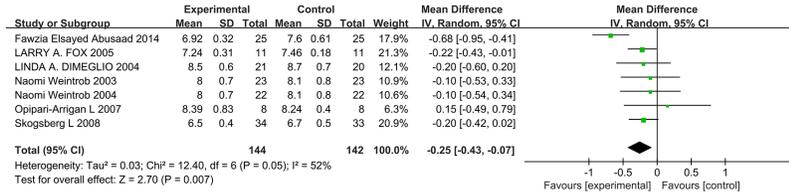
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**Figure legends**

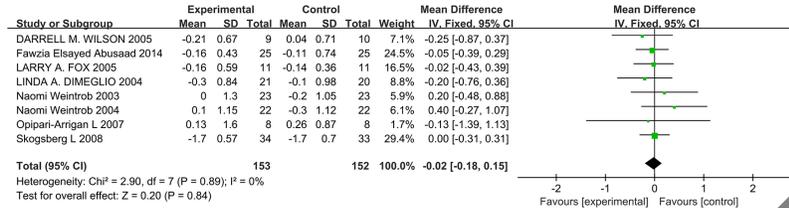


**Figure 1.** Flow diagram of the study selection process.

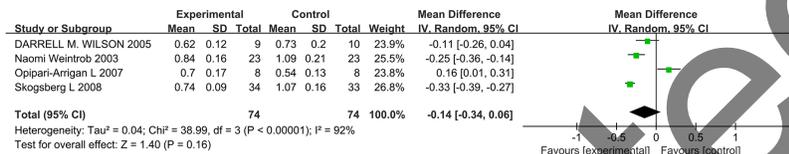
## A: HbA1c (%)



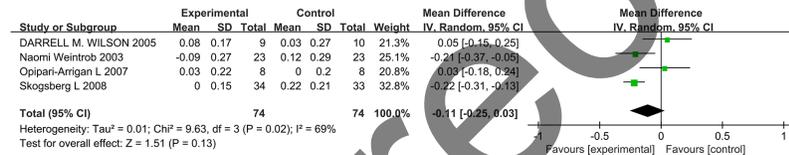
## B: HbA1c (%) change



## C: Total daily insulin doses per day



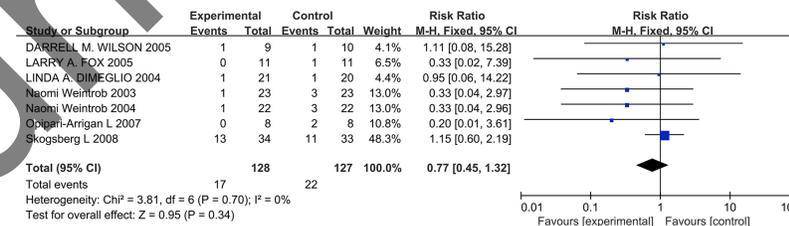
## D: Change of total daily insulin doses per day



## E: Ketoacidosis



## F: Severe hypoglycemia



**Figure 2.** Forest plots for meta-analysis on HbA1c (%) (A), HbA1c (%) change (B), total daily insulin doses per day (C), change of total daily insulin doses per day (D) and incidence of ketoacidosis (E) and severe hypoglycemia (F).

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