Effectiveness, Safety, and Parental Satisfaction of Insulin Pump Therapy Versus Multiple-Dose Injection Therapy in Preschool Children with Type 1 Diabetes: A Systematic Review and Meta-Analysis

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Abstract

Background: Despite the increasing demand for continuous subcutaneous insulin infusion (CSII) or insulin pump therapy in preschool children with Type 1 diabetes (T1D), reports on its advantages over conventional methods, particularly multiple dose injection (MDI) therapy, are scant. Objectives: We aimed to investigate the effectiveness, safety, and parental satisfaction of using CSII compared to MDI in preschool children with T1D. This study also seeks to establish criteria to help clinicians choose patients most suitable for CSII. Methods: Relevant terms based on the study outcomes were used to search electronic databases and manual search for the literature. Selected articles were then thoroughly reviewed and evaluated. Results: The effect in the meta-analysis showed a small, nonsignificant positive effect on HbA1c of the CSII compared to the MDI insulin intervention method (mean Cohen’s $d$ effect size = 0.25, Standard Error = 0.18, $P = 0.16$ ($n = 127$)) and a small, nonsignificant negative effect on safety of the CSII compared to the MDI insulin intervention method (mean Cohen’s $d$ effect size $= -0.26$, $SE = 0.36$, $P = 0.47$ [$n = 70$]). For parental satisfaction, data were small and therefore inappropriate for meta-analysis. Conclusion: For preschool children, the effectiveness and safety of insulin pump therapy compared with MDI therapy was considered statistically nonsignificant. All preschool children with T1D can be considered potentially eligible candidates for insulin pump therapy. Suggested selection criteria to apply when considering preschool children for insulin pump therapy were presented.

Keywords: Child, diabetes mellitus, insulin, insulin infusion systems, preschool, type 1

INTRODUCTION

The highest upsurge in the increasing incidence of Type 1 diabetes mellitus (T1DM) is observed among preschoolers. Parental treatment administration often causes psychological distress attributed to children’s normative misbehavior. In addition, T1DM management is not mastered by most parents. Continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy, has become a progressively standard mode of treatment for this age group as it offers some advantages over multiple dose injection (MDI) insulin therapy. Several better clinical outcomes of CSII over MDI have likewise been reported, including improvement in HbA1c and lower cardiovascular mortality. However, some associated adverse events were also observed, thereby negatively affecting its safety profile. Parental knowledge, in addition, is often noncomprehensive.

This study primarily aims to investigate the benefits of CSII versus MDI in preschool children in effectiveness, safety, and parental satisfaction. Effectiveness is described as the

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outcome of glycemic control; safety is assessed by minimal hypoglycemic effect, and parental satisfaction is defined as the enthusiasm to continue on CSII. Moreover, this study aims to suggest criteria to help clinicians choose suitable patients for CSII.

MATERIALS AND METHODS

Electronic manual search to identify all related articles in the following online databases CINAHL, MEDLINE (OVID), PubMed, Cochrane Library, Embase, Evidence NHS, PsycINFO, Scopus, NICE, Best Practice (BMJ) since there is no single source that provides all relevant literature. The following search parameters were used: (1) study objectives: randomized controlled trials (RCTs) and nonrandomized studies which discuss the selected outcomes, (2) participants: children 0–6 years of age with T1DM, (3) types of intervention: CSII in comparison with MDI, and (4) years of publication: the period from 1984 to February 2019 was chosen because it is unlikely to find any related studies before 1984.

The full texts of potentially relevant studies were retrieved and thoroughly examined by two reviewers. Forty-two records were identified. Thirty duplicates were removed, and seven additional studies were excluded. Five studies were included in the qualitative and quantitative analysis [Figure 1]. Data extraction was carried out independently by three reviewers. Discrepancies between the reviewers were resolved by discussion.

RESULTS

Random effects meta-analyses were performed for effectiveness (5 studies) and safety (3 studies) [Table 1], patients on MDI as the control group and patients on CSII as the intervention group. Studies that did not have a control and those with children in school age were not included.

Effectiveness

The effect size for all of the included studies corresponds to the difference in glycemic index measured as glycated hemoglobin (HbA1c) between intervention and control groups. The mean and standard deviation (SD) of HbA1c measured at all time points after baseline was grouped for the two study groups. It was deemed appropriate to, where possible, combine the HbA1c scores taken at different time points during the trials rather than use the final HbA1c outcome score, which was usually after 6 months. This is because the purpose of the intervention is the management of the disease over time.

Cohen’s $d$ effect sizes were calculated for each of the five studies included in the meta-analysis. The mean and SD for the difference in HbA1c between the baseline and follow-up were not reported in four of the five studies. This implies that the differences at baseline were not accounted for in the effect sizes for these studies. However, these studies reported no differences in HbA1c scores at baseline between randomized control and intervention groups. Due to this, it was assumed that the effect size reflects the difference between the two insulin treatment methods on HbA1c. Wilson et al., 2005 reported the mean difference in HbA1c between the baseline and follow-up stages for participants who completed the study, and so this result was used in the meta-analysis. Appendix 1 shows the information extracted from each study ahead of the meta-analysis, including Cohen’s $d$ effect size. Figure 2 is a forest plot showing the results of the fixed effect meta-analysis for the five controlled studies. The effect in the meta-analysis showed a small, nonsignificant positive effect of the CSII compared to the MDI insulin intervention method (mean Cohen’s $d$ effect size = 0.25, SE = 0.18, $P = 0.16 \ [n = 127]$).

A Cohen’s $d$ between 0.2 and 0.5 (such as the effect found in this meta-analysis) is considered a small effect size, an effect that may not be apparent when visually inspecting the data, but that nonetheless is clinically important. It has been suggested that actual clinically significant results have effect sizes of more than 0.4, and the effect size found in this study was smaller than the alternative value.

Safety

Four of the controlled studies reported the number of incidences when blood sugar levels dropped below a safe level (blood glucose below $<60$ mg/dL, $<5.6$ mmol/L and $<70$ mg/dL). These outcomes were deemed as similar measures of hypoglycemic incidents and therefore were included in the meta-analysis.

However, the results from Opipari-Arrigan et al., 2007 were not included in the analysis because the groups were significantly different at baseline, and the mean difference between baseline and follow-up was not reported. Including this study would be misleading because the difference in blood glucose level between the groups may be due to differences between participants within those groups observed at baseline.

Cohen’s $d$ effect sizes were calculated for each of the three studies included in the meta-analysis. The mean and SD difference in hypoglycemic effect between the baseline and follow-up were not reported in these three studies. For these studies, the differences at baseline were not accounted for in the effect sizes. However, studies were only included if they reported no differences between participants at baseline, and participants were randomized to the control and intervention groups. Due to this, it was assumed that the effect size reflects the difference between the two insulin treatment methods on the hypoglycemic effect.

Figure 3 is a forest plot showing the results of the fixed effect meta-analysis for the three controlled studies. The effect in the meta-analysis showed a small, nonsignificant negative effect on safety of the CSII compared to the MDI insulin intervention method (mean Cohen’s $d$ effect size = $-0.26$, SE = 0.36, $P = 0.47 \ [n = 70]$).

Parental satisfaction

Only two controlled studies offered enough data about parental satisfaction to be included in the meta-analysis. These studies used different questionnaires (parental stress index...
and diabetes quality of life [QoL] questionnaire). One of the noncontrolled studies\textsuperscript{[9]} also measured some aspects of parental satisfaction. However, since study participants were unblinded and this study was uncontrolled, it may have been biased. Given that only two controlled studies could be combined, the conclusions drawn from such a meta-analysis would be limited.

**Discussion**

All of the studies seemed to have included the MDI component, although the frequency may have differed. Questions may also be raised about whether the parents were already using this administration method before the beginning of each study and if the pump’s introduction was always new. Patient similarity may have also been an issue since there is a big difference between younger participants and older ones. Another factor may be differences in severity. Fox \textit{et al}., 2005,\textsuperscript{[27]} had patients with low glycemic index, therefore probably less severe than the other studies. Whether there are differences in the impact of CSII administration for more severe cases is unsettled. These factors influence the comparability of the studies. The random-effects meta-analysis model considers that each study is different and probably estimates a distinct “true” effect size. Therefore, the random-effects estimate (in this case, \(d = 0.25\)) estimates the mean of a normal distribution of true effect sizes.

The findings of Shehadeh \textit{et al}., 2004;\textsuperscript{[9]} Jeha \textit{et al}., 2005;\textsuperscript{[19]} and Litton \textit{et al}., 2002\textsuperscript{[18]} were not included in analyses because these did not directly specify control conditions such as learning factors or placebo effect. For the study of Nabhan \textit{et al}., 2009,\textsuperscript{[28]} only the results of up to 6 months were included because although the control group started using CSII after this duration, the CSII group did not cross over to intensive insulin therapy (IIT). The standard error and control condition means had to be extracted from the figure as no values were reported.
<table>
<thead>
<tr>
<th>First author name (date)</th>
<th>Outcome variable (s)</th>
<th>MDI (n)</th>
<th>CSII (n)</th>
<th>MDI (n)</th>
<th>CSII (n)</th>
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<th>CSII (n)</th>
</tr>
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<tbody>
<tr>
<td>DiMeglio, 2004</td>
<td>Effectiveness: Glycemic control (HbA1c) Safety: Hypoglycemic effect (proportion of observation when blood glucose values &lt;60 mg/dL) Parental stress: Parental stress index</td>
<td>17</td>
<td>20</td>
<td>MDI Baseline=8.8 (SD=0.7) Follow-up (3 and 6 months combined)=8.75 (SD=0.7) CSII Baseline=7.4 (SD=1.66) Follow-up (3 and 6 months combined)=8.22 (SD=0.99)</td>
<td>0.47 (95% CI 1.15-2.01) Var=0.11 (P=0.17) (small)</td>
<td></td>
<td></td>
<td>MDI Baseline=Did not measure Follow-up=3.9% (5.7/146) (small)</td>
<td></td>
<td></td>
<td>CSII Baseline=Did not measure Follow-up=5.5% (8.3/146)</td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Fox, 2005</td>
<td>Effectiveness: Glycemic control (HbA1c) Safety: Hypoglycemic effect (proportion of observation when blood glucose values &lt;60 mg/dL) Parental stress: Parental stress index</td>
<td>11</td>
<td>11</td>
<td>MDI Baseline=7.6 (SD=0.99) Follow-up (3 and 6 months combined)=7.46 (SD=0.66) CSII Baseline=7.4 (SD=1.66) Follow-up (3 and 6 months combined)=8.22 (SD=0.99)</td>
<td>0.29 (95% CI 0.61-1.18) Var=0.18 (P=0.51) (small)</td>
<td></td>
<td></td>
<td>MDI Baseline=40% 48/120 Follow-up=25.8% (31/120) (medium)</td>
<td></td>
<td></td>
<td>CSII Baseline=21.6% (26/120) Follow-up=59.2% (71/120)</td>
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<td></td>
<td>Measured but not reported</td>
<td>Measured but not reported</td>
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<tr>
<td>Nabhan, 2009</td>
<td>Effectiveness: Glycemic control (HbA1c) Parental stress: Parental stress index</td>
<td>17</td>
<td>18</td>
<td>MDI Baseline: 8.9 (SD=0.6) Follow-up (3 and 6 months combined)=8.86 (SD=0.68) CSII Baseline: 8.8 (SD=0.6) Follow-up (3 and 6 months combined)=8.45 (SD=0.89)</td>
<td>0.52 (95% CI 0.18-1.22) Var=0.12 (P=0.14) (medium)</td>
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<td></td>
<td>MDI Baseline=77.4 (SD=29.6) Follow-up=71.9 (SD=26.1) (large)</td>
<td></td>
<td></td>
<td>CSII Baseline=77.4 (SD=29.6) Follow-up=71.9 (SD=26.1) (large)</td>
<td></td>
<td></td>
<td>Measured but not reported</td>
<td>Measured but not reported</td>
</tr>
<tr>
<td>Opipari-Arrigan, 2007</td>
<td>Effectiveness: Glycemic control (HbA1c)</td>
<td></td>
<td></td>
<td>MDI Baseline: 7.98 (SD=0.76) Follow-up (6 months)=8.24 (SD=0.4)</td>
<td>−0.24 (95% CI −1.42-0.94) Var=0.29 (P=0.66) (small)</td>
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<td></td>
<td>MDI Baseline=0.59 (SD=0.32) Follow-up=0.85 (SD=0.58) (no effect)</td>
<td></td>
<td></td>
<td>MDI Baseline=77.4 (SD=29.6) Follow-up=71.9 (SD=26.1) (large)</td>
<td></td>
<td></td>
<td>−0.89 (95% CI −2.12-0.35) Var=0.32 (P=0.14) (large)</td>
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Contd...
### Table 1: Contd...

<table>
<thead>
<tr>
<th>First author name (date)</th>
<th>Outcome variable(s)</th>
<th>MDI (n)</th>
<th>CSII (n)</th>
<th>Effectiveness, mean or % (SD, or proportion) of outcome variable for intervention group</th>
<th>Safety, mean or % (SD, or proportion) of outcome variable for intervention group</th>
<th>Parental stress, mean or % (SD, or proportion) of outcome variable for intervention group</th>
<th>Cohens d, variance (size)</th>
<th>Cohens d, variance (size)</th>
<th>Cohens d, variance (size)</th>
</tr>
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<tbody>
<tr>
<td>Wilson, 2005</td>
<td>Effectiveness: Glycemic control (HbA1c) Safety: Hypoglycemic effect (percentage of instances when blood glucose &lt;5.6 mmol/L) Parental stress: PIP difficulty total</td>
<td>10</td>
<td>9</td>
<td>MDI (mean difference to baseline) 0.04 (SD=0.71) CSII (mean difference to baseline) 0.21 (SD=0.67) −0.25 (95% CI=−1.22−0.73) Var=0.21 (P=0.6) (small)</td>
<td>MDI Baseline=17 (SD=8) Follow-up=20 (SD=6) 0.17 (95% CI=−0.8−1.14) Var=0.21 (P=0.72) (no effect)</td>
<td>MDI (mean difference to baseline) −0.08 (SD=0.19) CSII (mean difference to baseline) −0.24 (SD=0.25)</td>
<td>0.71 (95% CI=−0.28−1.71) Var=0.22 (P=0.15) (medium)</td>
<td>0.17 (95% CI=−0.8−1.14) Var=0.21 (P=0.72) (no effect)</td>
<td>0.71 (95% CI=−0.28−1.71) Var=0.22 (P=0.15) (medium)</td>
</tr>
</tbody>
</table>

**SD:** Standard deviation, **CI:** Confidence interval, **N/A:** Not applicable, **DQOL:** Diabetes quality of life, **PIP:** Pediatric inventory for parents, **MDI:** Multiple-dose injection, **CSII:** Continuous subcutaneous insulin infusion, **Var:** Variance
in the text. This may impact the precision of the results of this study. Moreover, the baseline PSI results were not reported by the group that the parents were in. Thus, while comparing parents’ stress in IIT versus CSII groups as possible, there seemed to be no method to compare their baseline levels of stress. Therefore, the difference, or lack thereof, of PSI scores between parents in the intervention and control groups was impossible to interpret without assuming their similarity or difference at the beginning of the trial. Thus, this study was not included in the meta-analysis with other controlled studies due to a lack of control on this aspect. Fox et al., 2005,[27] likewise failed to report the actual scores for the parental stress index; therefore, only two sets of results were left, making meta-analysis unbeficial.

Below targets baseline of glucose concentrations was used in the study of Wilson et al. 2005,[24] combined with two other studies that measure the proportion of blood sugar level <60, the measurement of the same parameters (e.g., the proportion of times participants dropped below safe blood sugar levels) was assumed. The glucose events from the study of Opipari-Arrigan, et al., 2007,[23] were not included in the meta-analysis because the groups were significantly different at baseline, and the mean difference between baseline and follow-up was not reported. When performing a meta-analysis, it is common to use and analyze a funnel plot to judge whether or not there has been publication bias. This was not done because only three and five studies were included in the meta-analyses, and the two studies showed a negative effect in each analysis.

The insulin pump has probably been considered less safe for preschool children because studies have not used the latest insulin pump, which has a feature of “before low suspend.” With the new technology, which has hypoglycemia alerts, alarms and insulin suspend feature, the insulin pump may be safer for preschool children than MDI.

An obvious limitation of this review is the small sample size which may not represent the general population of preschool children with T1DM. Only a few RCTs studied this specific age group (preschool children) separately. Despite that they are recent, other RCTs mixed older children with preschool children, which made it impossible for us to separate them from the rest of the group. This also reduced the power of statistical analyses to detect significant differences.

It is well known that improvement of HbA1c is mainly related to the effectiveness of glucose monitoring; however, there was no mention of glucose monitoring devices used in the RCTs. Moreover, time in range (TIR) would have been more informative, but the studies included in our analysis were carried out before we started using TIR.

**CONCLUSIONS**

As there are no CSII selection criteria for this age group, a few conclusions emerge from this review. First, parents need to have realistic expectations of CSII on optimizing basal/bolus therapy, reducing recurrent severe hypoglycemia, and reducing recurrent ketoacidosis; second, regarding psychological aspects, the need to agree between parent and the team, strong parental motivation, and capacity to use the pump; and third, concerning educational factors, parents need to be educated on the insulin pump to learn the basics of dealing with an insulin pump, safety and basics of carbohydrate counting, dose adjustments, frequency of blood sugar testing, and how to deal with daily changes. Further research for a longer duration and the use of a multicentre approach to study larger populations of preschool children with T1DM may be the best way to provide more significant results and to assess long-term outcomes of CSII use. A standard QoL questionnaire should also be developed for parents of preschool children with T1DM.

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**Authors’ contribution**

All authors contributed substantially to the study by literature search, data analysis, drafting and revising of the manuscript and approval of its final version.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**Compliance with ethical principles**

No formal ethical approval is required for systematic review–meta-analysis type of study.

**References**


