Journal of Diabetes Science and Technology
Volume 4, Issue 4, July 2010

ORIGINAL ARTICLES

Pilot Study for Assessment of Optimal Frequency for Changing Catheters in Insulin Pump Therapy—Trouble Starts on Day 3

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Abstract

Background:

Continuous subcutaneous insulin infusion (CSII) by means of insulin pump devices is considered to be one of the most optimal therapies to achieve treatment targets in patients with diabetes mellitus. In CSII, the insulin is delivered through Teflon catheters or steel needle infusion sets, which need to be renewed on a regular basis. This pilot study was performed to investigate the optimal change frequency in daily practice and to explore potential problems that may occur when the sets are used for a more prolonged time than the recommended up to 72 hours of usage (Teflon catheters).

Method:

Twelve patients with type 1 diabetes participated in the trial [age (mean ± STD): 40.3 ± 12.6 years, body mass index: 26.2 ± 3.3 kg/m², hemoglobin A1c: 6.7 ± 0.6%]. They were asked to wear their infusion set (Comfort™ or Silhouette®) for increasing periods of 1, 2, 3, 4, and 5 days. After each use, patients completed standardized questionnaires regarding technical and medical issues associated with infusion set use. A health care professional investigated the infusion sites and infusion sets and completed an "infusion set inspection" questionnaire. Blood glucose was measured and recorded to assess a potential influence of duration of catheter use on glycemic control.

Results:

Infusion set and injection site problems (itching, bruising, swelling, and pain) started to occur in measurable amounts on the 3rd day of catheter use, and about 40% of patients reported significant issues when using a catheter for 5 days. In parallel, there was a consistent increase in mean daily blood glucose levels that correlated with the number of days of catheter use (e.g., day 1: 7.5 ± 3.8 mmol/liter, day 3: 8.4 ± 4.2 mmol/liter, day 5: 9.0 ± 4.0 mmol/liter, day 7: 11.6 ± 2.2 mmol/liter, $p < 0.05$ vs day 1).

Conclusions:

Using the catheters for 2 days resulted in a safe and well-tolerated therapy. Clinically relevant adverse events started to occur during the 3rd day and their incidence increased constantly with longer use. This was associated with undesired changes in mean glycemic control. Data support the recommendation by the drug and device manufacturers that insulin pump catheters should only be used for 48–72 hours to avoid adverse events and potential metabolic deterioration.

J Diabetes Sci Technol 2010;4(4):976-982

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Abbreviations: (BG) blood glucose, (CSII) continuous subcutaneous insulin infusion, (DKA) diabetic ketoacidosis, (HbA1c) hemoglobin A1c

Keywords: CSII, catheter infusion set, duration of use, infusion set failure, insulin pump therapy

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Introduction

Continuous subcutaneous insulin infusion (CSII) by means of insulin pump devices is considered to be the most optimal method to achieve near-normal blood glucose (BG) levels in patients with type 1 diabetes.[1,2] In addition, it has also been applied successfully to patients with type 2 diabetes.[3,4] Therefore, the number of pump users is increasing worldwide, despite the economic and technological challenges associated with this kind of insulin therapy. It is estimated that more than 500,000 patients worldwide are currently being treated with CSII. In many countries, the prerequisites for successful CSII therapy are considered to be manifold and include, but are not limited to, comprehensive patient education and understanding of intensive insulin therapy, frequent review and analysis of daily glucose values and insulin delivery parameters by the patient and his/her physician, and appropriate changes of the insulin infusion sets on a regular basis.[5]

Catheter manufacturers and insulin manufacturers recommend changing infusion sets and infusion sites every 48–72 hours in order to avoid skin irritations, infusion site reactions, and other undesired side effects of CSII therapy. However, these infusion site-related recommendations are based on reports derived from anecdotal data sets about use of the infusion set in daily practice, and thorough investigations providing a scientific rationale for depicting a safe interval for the changes are still lacking to date. It has been shown in different investigations that regular human insulin, insulin glulisine, insulin aspart, and insulin lispro can be applied safely in CSII when infusion sets are changed every 2 days.[6–10]

Potential problems that may occur in adult and adolescent patients when using infusion sets longer than the recommended 48–72 hours may be bacterial contaminations leading to skin inflammations,[11–13] potential changes in physicochemical delivery characteristics,[14,15] and catheter occlusions.[16,17] With all three short-acting insulin analogs, Kerr and colleagues[16] demonstrated that early catheter occlusions (within 72 hours) are rare and independent of the choice of insulin analog. The authors concluded that for patients using insulin pump therapy, the importance of catheter change within 72 hours should be emphasized irrespective of the insulin used.[16]

The purpose of this pilot study was to investigate the impact of using CSII infusion sets (Silhouette® and Comfort™) for 5 days or more on glycemic control and the occurrence of adverse events in patients with type 1 diabetes.

Patients and Methods

Study Population

Twelve type 1 diabetes mellitus patients were enrolled in this study. Inclusion criteria were type 1 diabetes, age between 18 and 75 years, experience with continuous insulin infusion for at least 3 months, and current therapy with insulin lispro (Humalog®). Exclusion criteria were significantly raised laboratory safety parameters (2.5 times above the normal reference range of one of the following parameters: creatinine, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, γ-glutamyltransferase, leukocytes, erythrocytes, platelets, hematocrit), hypersensitivity or allergy to insulin lispro (Humalog), or clinically significant physical findings, as well as mental, physical, or legal incapacity jeopardizing the compliance of patients. Women of child-bearing potential not actively and consistently practicing birth control in an appropriate manner, pregnant, and breast-feeding women were also excluded. Prior to study participation, patients were informed about study details, both verbally and in written form. The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the declaration of Helsinki and the applicable guidelines for good clinical practice, whichever provided the greater protection of the individual. Additionally, the study was approved by the ethics committee of Mainz (Landesärtzekammer Rheinland-Pfalz, Germany) and conducted in accordance with all applicable German laws and regulations.

Study Design

This study was designed as an open, prospective, exploratory, and single-center study. Patients were asked to apply five catheters, each for an increasing time period of 1, 2, 3, 4, and 5 days. The fifth catheter was to be applied for at least 5 days and up to 7 days. In total, study participation lasted 15 to 17 days in case that no safety problems arose necessitating a premature catheter exchange.

Catheter Application

Depending on the insulin pump type, either the Comfort or the Silhouette (manufactured by Unomedical a/s, DK- 4320 Lejre, Denmark) infusion set was used

(Comfort for luer lock pump connector, Silhouette for the propriety connector). The soft cannula (indicated with a "1" in **Figure 1**) was applied at an angle of 20 to 45° and rested in the cannula housing on the skin by a built-in adhesive (2), which secured the cannula in place. The connector (3) connected the tubing to the cannula housing (4). The reservoir connector (5) connected the tubing to the pump (not displayed in **Figure 1**). Cannulas of subsequent catheters were inserted around the umbilicus in a clockwise manner. All patients used the insulin pump they applied routinely. Individual insulin pump dose schedules or insulin pump therapy plans were not modified. To allow for catheter exchanges for safety reasons, patients additionally received a safety infusion set at visit 1.

Evaluation of Catheter Comfort and Performance, Injection Site, and Infusion Set

To assess all parameters relevant to "comfort and performance," the "injection site," and the "infusion set," three corresponding standardized questionnaires had to be completed. In parallel, a health care professional inspected the infusion sets and completed an "infusion set inspection" questionnaire.

Safety Measurements

To control levels of BG in a more standardized fashion, all patients were provided with the same blood glucose meter (Precision Xceed, Abbott MediSense, Wiesbaden, Germany) and appropriate number of test strips at visit 1. Patients were asked to measure their blood glucose levels frequently with the provided BG meter. They had to conduct at least seven daily measurements scheduled before and after meals (assuming three meals per day) and one assessment before going to bed. For assessment of the laboratory safety parameters described earlier, venous blood was drawn at screening visit 2 up to 14 days prior to visit 1 and at visit 10.

Results

Patient Characteristics

Of the 12 screened and enrolled subjects, all were of Caucasian origin. The gender assignment was four male (33.3%) and eight female (66.7%) patients. The age of the patients ranged from 22 to 64 years and was, on average, 46.8 ± 17.9 (mean ± SD) for male patients and 37 ± 8.7 (mean ± SD) for female patients. Detailed demographic data of the patients are provided in Table 1. Eight out of 12 patients were currently using an insulin pump from Roche Diagnostics, whereas the remaining 4 patients applied the Paradigm pump from Medtronic MiniMed. Only 1 patient had previous experience with pumps from both companies. The vast majority of patients had only used one insulin pump prior to the study (6× Roche; 3× MiniMed; 1× "other"). Six patients had experience with both steel and Teflon infusion sets, while the other half had exclusively used one needle type before (3× steel; 3× Teflon). Regarding the choice for infusion sites, the most frequent injection site was the abdomen (10 patients). Hips (5 patients) and buttocks (6 patients) were also used quite often, while the thigh was only selected once and the arm was not selected at all for injection. Eight patients preferred the abdomen, 3 the hips, and 1 each the buttocks or the thighs. Eight patients routinely changed the body part for a new catheter application, while 4 did not. Seven patients selected injection sites according

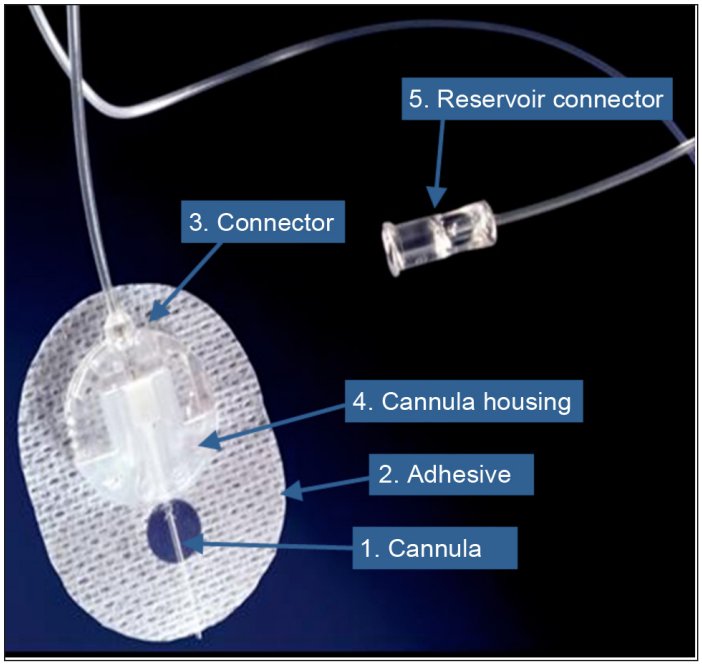

Figure 1. The Unomedical Comfort™ infusion set with its individually labeled parts..

Table 1.
Characteristics of Patients (n = 12) Enrolled in Study

Parameter	Mean ± standard deviation
Age (years)	40.3 ± 12.6
Height (centimeter)	172.6 ± 9.8
Weight (kilogram)	78.3 ± 13.7
Body mass index (kg/m^2)	26.2 ± 3.3
Systolic blood pressure (mm Hg)	124.2 ± 15.5
Diastolic blood pressure (mm Hg)	76.1 ± 7.7

to a fixed injection schedule (e.g., a clockwise pattern). Replacing the infusion sets and connecting the tubes to the inserted catheter were classified to be "easy" or "very easy" by all 12 patients. The mean catheter usage time of all patients before the study was reported to be 2.5 ± 0.8 days.

Previous experience with skin irritations at the insertion site was rated by 50.8% as "never," 42.4% as "rarely," 5.1% as "sometimes," and once as "often." Premature changes (i.e., changes before the time point predefined by the protocol) of infusion sets occurred nine times during this study. The reasons were leakage (five times), skin irritation (two times), kinking (one time), and skin inflammation (one time).

An increased prevalence of redness at the infusion site as a signal for local skin irritation as assessed by the investigator occurred most frequently between days 2 and 3 of catheter use. However, the classical inflammatory sign of tissue "swelling" was only observed for one patient, who exhibited a swelling with a diameter of 2 mm after a continuous infusion set application for 6 days. The percentage of patients showing infusion site findings when assessed by the investigator is provided in **Figure 2**.

The first and second catheters were used by all patients for the intended time period of 1 and 2 days, respectively, without any report of adverse events. The third catheter—intended for 3-day use—was replaced prematurely by three patients (25%) because of adverse events. The same result was seen when patients used the infusion set for 4 days. Finally, only seven patients (58%) managed to use the fifth catheter for 5 or more days. There was no association between the appearance of adverse events and individual patients in this study. Bruising around the injection site was reported in two cases (after 4 and 7 days of catheter use, respectively). Summarizing all reported adverse events, the Kaplan–Meier curve for using the infusion set without any event in correlation with the period of use is provided in **Figure 3**. Time to the first appearance of observed clinical and technical events is shown in **Table 2**. It can be seen from both presentations that infusion sets were used without problems for 2 days and that events started to appear more frequently during and after the 3rd day of use.

In total, 59 Teflon catheters were inspected after use for any sign of abnormal functioning. There were no cases of crimping, and one case of kinking of the catheter tip led to premature catheter exchange. Occlusion of tubing

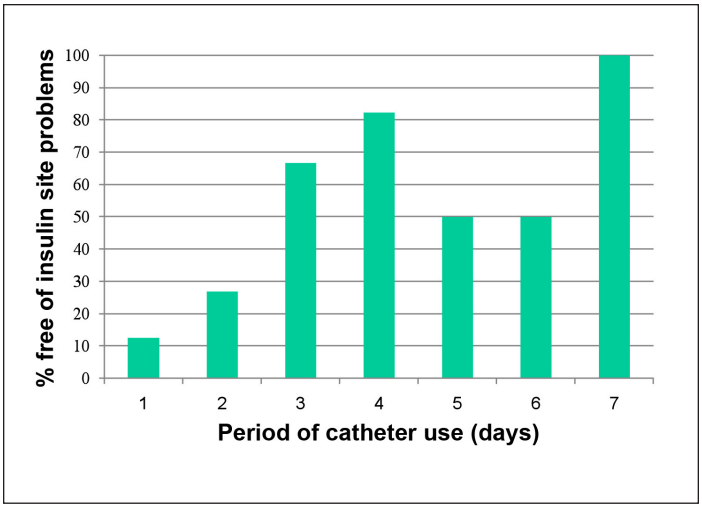

Figure 2. Percentage of patients with treatment-emerged adverse events as assessed by the investigator for different time periods of catheter use.

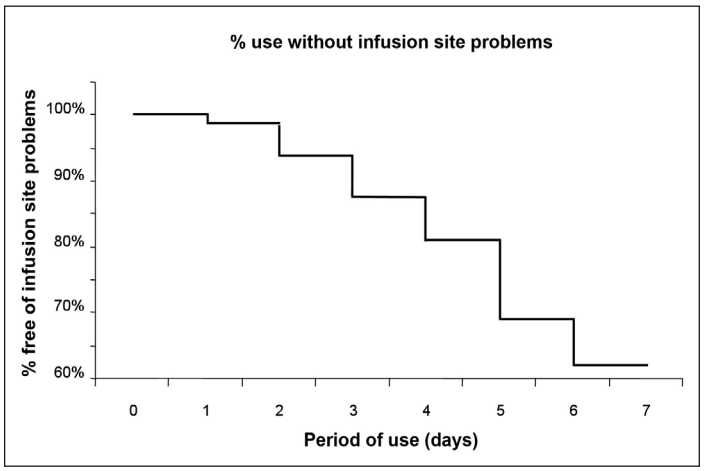

Figure 3. Kaplan–Meyer curve of patients free from treatment-emerged adverse events.

sets leading to a pump alarm was seen in two cases, also resulting in premature termination of the catheter use at day 2 and day 3, respectively, instead of the anticipated use for 5 days. Finally, the average duration of infusion system use observed in this study was 2.8 ± 0.8 days.

Figure 4 provides mean values of daily BG levels as assessed by seven-point profiles in relation to different application periods of individual catheters. There was no change in eating behavior during participation in the study as assessed by reviewing the carbohydrate count information entered by patients into their personal diabetes diaries. It is remarkable that the mean BG concentrations increased in close correlation with the duration of catheter usage. In our study, the difference reached the level of statistical significance finally on day 7. It needs to be clarified though that only a few patients

Table 2.
Time to First Appearance of Investigated Clinical and Technical Events When Assessed by Investigator[a]

Reason for unscheduled catheter change	Day of Use						
	1	2	3	4	5	6	7
Pulling out of soft cannula							
Crimping of soft cannula							
Kinking of soft cannula							
Occlusion of soft cannula							
Occlusion of tubing							
Adhesive falling off							
Adhesive becoming loose							
Leakage of cannula							
Insulin leakage from tubing							
Insulin leakage from injection site							
Bleeding into infusion set							
Bruising around injection site							
Infection around injection site							

[a] Light blue boxes indicate the day on which a first event was observed.

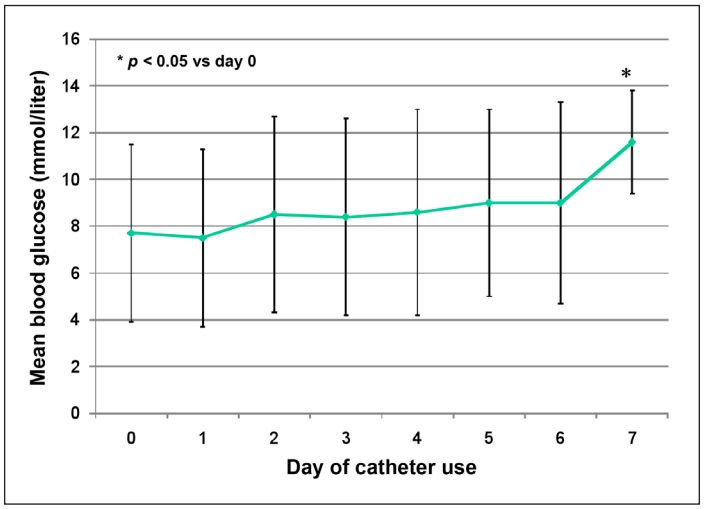

Figure 4. Mean blood daily glucose values (in mmol/liter) derived from seven-point blood glucose profiles performed by patient self-measurement during application of catheters. Means (± standard deviation) are shown for all catheters.

were really reaching more than 5 days of catheter use in this pilot trial.

No serious adverse events were reported in the trial, and none of the safety laboratory parameters showed a clinically relevant deviation from normal reference values.

Discussion

More than three decades after its introduction, the use of CSII keeps increasing, especially among children and adolescents. When used properly, the treatment is considered to be safe and effective. Compared with traditional neutral protamine Hagedorn-based multiple daily injections, CSII provides a clinically important reduction of hemoglobin A1c (HbA1c) levels,[18] reduces blood glucose variability,[19] decreases severe hypoglycemic episodes,[18,19] offers a better way of coping with the dawn phenomenon,[1] and has a positive impact on the quality of life.[18] CSII is considered to be particularly beneficial for patients experiencing severe hypoglycemic episodes, high HbA1c values, or marked glucose variability while being treated with intensive insulin therapy.[2] An increased risk for diabetic ketoacidosis (DKA) in patients with type 1 diabetes using pump therapy has been well documented in the literature.[20] Insulin delivery may be disrupted accidentally by cannula or tubing occlusion; the cannula becoming dislodged; battery failure or air pockets in the tubing; cloudy, crystallized, or expired insulin; or programming malfunction. This may particularly happen if users leave an infusion set in place too long (>72 hours), which can lead to impaired insulin absorption.[5] Whatever the

cause of disrupted insulin delivery, DKA is more likely to develop when patients do not know how to respond properly to hyperglycemia. Therefore, education and training play a critical role in preventing DKA among pump users,[21] and infusion site management in pump therapy extends beyond site rotation. Bacterial infusion site infection and contact dermatitis caused by infusion set adhesive, although rare, can arise in the context of insulin pump therapy. Infusion site infections are caused most often by Streptococcus bacteria that have seeded from the skin flora, but Staphylococcus species and other pathogens may also be involved, particularly in staph carriers.[22,23] All these deteriorations may contribute to a gradual impairment of glycemic control over a prolonged use of infusion sets in CSII. There is a tendency in the reimbursement systems of some countries to direct patients into a more prolonged use of an insulin pump catheter by a more restrictive reimbursement policy. We, therefore, believe it is important to reconsider the potential medical consequences for the patient.

Our pilot study investigated the incidence of all the aforementioned infusion set-related events in correlation with the duration of catheter use. While all patients could safely use the infusion sets for at least 2 days, multiple problems started to occur on the 3rd day, partly requiring a change of the infusion sets. There was no single specific event related to extended catheter use, but events of all kinds and nature occurred after day 3, including, but not limited to, pulling out, kinking, adhesive getting loose, leakage from the infusion set or the infusion site, and signals of skin irritation such as bruising, redness, or swelling. Even when patients locally tolerated a longer use of the infusion sets at the infusion site for up to 7 days, there appeared to be changes in insulin absorption, leading to a slow but steady loss in glycemic control with increased duration of use, as indicated by a steady increase in mean daily BG concentrations.

Our study is a pilot trial and therefore has several limitations. First, the number of patients is too small and the observed findings are to incidental to confirm any significant conclusion and may only serve to generate hypotheses for further confirmatory trials. Second, the blood glucose readings were performed by the patients themselves, which may have an impact on data quality. Finally, the duration of use was not randomized but increased stepwise, which may also have influenced the study outcome.

In any case, and even under consideration of the pilot nature of the trial, it can be stated clearly that safe and effective insulin pump therapy can only be warranted when patients follow the recommendation to change their infusion sets and the infusion site regularly after 48–72 hours of use in order to avoid skin reactions and technical problems with pump and tubing, and to ensure a stable and reliable efficacy of the applied insulin.

Funding:

This study was funded by an unrestricted grant from Unomedical, Leijre, DK.

Acknowledgment:

The author acknowledges the commitment of the study participants and the extraordinary performance of the medical team of IKFE in conducting this study.

Disclosure:

Thomas Forst has received research grants from Unomedical. Andreas Pfützner is a member of the scientific advisory board of Unomedical and has received consultancy fees and research grants from Unomedical.

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