Health-Related Quality of Life, Treatment Satisfaction, and Costs Associated With Intraperitoneal Versus Subcutaneous Insulin Administration in Type 1 Diabetes

A randomized controlled trial

Susan J. Logtenberg, MD, PHD[1]
Nanne Kleefstra, MD[1,2]
Sebastiaan T. Houweling, MD, PHD[1,2,3]
Klaas H. Groenier, PHD[4,5]
Reinold O. Gans, MD, PHD[5,6]
Henk J. Bilo, MD, PHD, FRCP[1,5,6]

OBJECTIVE — To investigate the effects of continuous intraperitoneal insulin infusion (CIPII) compared with subcutaneous insulin on health-related quality of life (HRQOL) and treatment satisfaction, and to perform a cost analysis in type 1 diabetes.

RESEARCH DESIGN AND METHODS — We used an open-label, prospective, crossover, randomized, 16-month study ($N = 24$). HRQOL and patient satisfaction were assessed with questionnaires (the 36-item short-form health survey [SF-36], the World Health Organization-Five Well-Being Index [WHO-5], and the Diabetes Treatment Satisfaction Questionnaire [DTSQ]). Direct costs of CIPII and continuous subcutaneous insulin infusion (CSII) were compared.

RESULTS — Questionnaire scores were higher with CIPII than with subcutaneous therapy. Yearly direct pump- and procedure-associated costs for CIPII were estimated at €10,910 compared with €4,810 for CSII.

CONCLUSIONS — Apart from improving glycemic control, CIPII improved HRQOL and treatment satisfaction compared with subcutaneous insulin. Direct pump- and procedure-associated costs are considerably higher for CIPII, however.

Diabetes Care 33:1169–1172, 2010

We recently showed that treatment with continuous intraperitoneal insulin infusion (CIPII) compared with subcutaneous insulin results in better glycemic control, expressed as a 0.8%-point decrease in A1C (1). The aim of the current analysis was to assess the effects of CIPII on health-related quality of life (HRQOL) and treatment satisfaction compared with intensified subcutaneous insulin therapy, and to provide up-to-date cost calculations of direct pump- and procedure-associated costs.

RESEARCH DESIGN AND METHODS

— The investigator-initiated study had a crossover, randomized design and was conducted in the Isala Clinics in the Netherlands. The design has been described in detail previously (1). In brief, adult subjects with type 1 diabetes, inadequately controlled with subcutaneous insulin regimens, were randomized to receive either 6 months of subcutaneous insulin therapy followed by 6 months of CIPII, or vice versa. Subcutaneous insulin was delivered with either multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII), whatever the patient used prior to the study.

Informed consent was obtained from all patients. The protocol was approved by the local ethics committee.

For HRQOL assessment, the the 36-item short-form health survey (SF-36) and the the World Health Organization-Five Well-Being Index (WHO-5) questionnaires were used. The SF-36 is a widely used, generic questionnaire with 36 items involving eight subscales and a physical and mental component summary (PCS and MCS, respectively). Scale scores range from 0–100, with higher scores indicating better HRQOL (2,3). The WHO-5 is designed to measure positive well-being and is reported to be better in identifying depression than the SF-36 MCS (4,5). It consists of five items with a total score ranging from 0–100. A score below 50 suggests poor emotional well-being (6).

Treatment satisfaction was measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ). All eight items are scored on a 7-point scale. Two items assess perceived frequency of hyperglycemia and hypoglycemia, and six items comprise the treatment satisfaction scale, with higher scores indicating higher satisfaction (range 0–36) (7).

Cost calculations were done using the Dutch manual for costing as a guideline and using local 2007 protocols and prices (8). No comparison with costs for MDI was made. For CSII treatment, prices were used for the most frequently used pump and its accessories in our hospital region: the Paradigm 512/712 (Medtronic/Minimed, Northridge, CA). Usage of medical consumables like insulin infusion sets and reservoirs was based

From the [1]Diabetes Centre, Isala Clinics, Zwolle, the Netherlands; the [2]Langerhans Medical Research Group, Zwolle, the Netherlands; the [3]General Practice Sleeuwijk, Sleeuwijk, the Netherlands; the [4]Department of General Practice, University Medical Center Groningen, Groningen, the Netherlands; [5]University of Groningen, Groningen, the Netherlands; and the [6]Department of Internal Medicine, University Medical Center Groningen, Groningen, the Netherlands.
Corresponding author: Susan Logtenberg, s.j.j.logtenberg@isala.nl.
Received 21 September 2009 and accepted 16 February 2010. Published ahead of print at http://care.diabetesjournals.org on 25 February 2010. DOI: 10.2337/dc09-1758. Clinical trial reg. no. NCT00286962, clinicaltrials.gov.

Table 1—*Health related quality of life and treatment satisfaction baseline and outcome*

	Baseline		Period 1			Period 2		Treatment mode		Treatment effect	
	Group A	Group B	CIPII (group A)	SC insulin (group B)	*P*	SC insulin (group A)	CIPII (group B)	CIPII	SC insulin	Adjusted for treatment order *	*P*
n	11	12						23	23		
SF-36 subscales											
Physical functioning	67.7 ± 24.0	76.7 ± 19.9	72.7 ± 23.6	69.6 ± 24.4	0.76	58.2 ± 24.1	80.4 ± 21.2				
End of treatment phase								76.7 ± 22.2	64.1 ± 24.4	12.7 (4.8, 20.5)	<0.01
Change from baseline (%)								+6.0	−11.4†		
Social functioning	63.6 ± 21.3	62.5 ± 25.0	68.2 ± 27.0	63.5 ± 30.4	0.70	56.8 ± 28.2	77.1 ± 28.1				
End of treatment phase								72.8 ± 27.3	60.3 ± 28.9	12.5 (−0.7, 25.6)	0.06
Change from baseline (%)								+15.5	−4.3		
Role limitations: physical	50 (25,75)	62.5 (0, 94)	50 (0, 100)	37.5 (0, 100)	0.68	0 (0, 50)	87.5 (31.3, 100)				
End of treatment phase								60.9 ± 41.9	35.9 ± 43.8	25.1 (8.0, 42.1)	<0.01
								75 (25, 100)	0 (0, 100)		
Change from baseline (%)								+55.6†	−8.3		
Role limitations: emotional	100 (0–100)	83.3 (8.3, 100)	100 (100, 100)	100 (8.3, 100)	0.24	66.7 (33.3, 100)	100 (75, 100)				
End of treatment phase								82.6 ± 36.1	65.2 ± 42.0	17.6 (3.6, 31.5)	0.02
								100 (100, 100)	100 (33.3, 100)		
Change from baseline (%)								+23.9†	−2.2		
Mental health	74.5 ± 16.4	61.3 ± 25.7	77.8 ± 16.4	63.0 ± 25.4	0.11	67.3 ± 15.4	72.3 ± 19.4				
End of treatment phase								75.0 ± 17.9	65.0 ± 20.8	9.9 (3.3, 16.6)	<0.01
Change from baseline (%)								+10.8†	−3.9		
Vitality	44.5 ± 17.4	45.0 ± 26.3	55.5 ± 21.1	45.0 ± 23.1	0.27	32.7 ± 17.5	60.4 ± 21.0				
End of treatment phase								58.0 ± 20.8	39.1 ± 21.1	19.1 (9.8, 28.3)	<0.01
Change from baseline (%)								+29.6†	−12.6		
Bodily pain	58.8 ± 24.9	59.2 ± 27.4	56.9 ± 29.4	56.5 ± 33.5	0.98	58.1 ± 31.0	65.3 ± 19.2				
End of treatment phase								61.3 ± 24.4	57.3 ± 31.6	3.8 (−7.9, 15.5)	0.50
Change from baseline (%)								+3.9	−2.9		
General health	33.0 ± 14.5	45.8 ± 18.2	51.9 ± 20.0	44.2 ± 21.6	0.38	40.0 ± 20.5	54.4 ± 16.9				
End of treatment phase								53.2 ± 18.1	42.2 ± 20.7	11.1 (3.1, 19.1)	<0.01
Change from baseline (%)								+34.1†	+6.2		
SF-36 summary scores											
PCS	34.7 ± 10.0	42.4 ± 8.6	39.2 ± 11.7	39.7 ± 11.2	0.92	34.6 ± 13.7	44.7 ± 8.5				
End of treatment phase								42.1 ± 10.3	37.3 ± 12.4	4.8 (0.8, 8.9)	0.02
Change from baseline (%)								+8.7	−3.8		
MCS	48.8 ± 10.7	42.5 ± 14.5	52.0 ± 11.8	44.5 ± 13.8	0.18	44.9 ± 10.8	49.8 ± 12.1				
End of treatment phase								50.8 ± 11.7	44.7 ± 12.2	6.2 (2.1, 10.3)	<0.01
Change from baseline (%)								+11.7†	−1.9		
WHO-5 score											
Score	48.4 ± 21.6	43.7 ± 26.6	67.6 ± 22.4	45.0 ± 25.6	0.04	45.5 ± 20.2	62.3 ± 23.6				
End of treatment phase								64.87 ± 22.69	45.2 ± 22.7	19.8 (9.9, 29.6)	<0.01
Change from baseline (%)								+41.3†	−1.5		
DTSQ											
Total score	25.5 ± 6.3	22.3 ± 7.8	34.0 ± 2.1	24.0 ± 6.5	<0.001	22.6 ± 11.7	31.3 ± 4.8				
End of treatment phase								32.6 ± 3.9	23.3 ± 9.2	9.3 (4.8, 13.9)	<0.01
Change from baseline (%)								+37.2†	−1.6		

Table 1—*Continued*

	Baseline		Period 1			Period 2		Treatment mode		Treatment effect	
	Group A	Group B	CIPII (group A)	SC insulin (group B)	*P*	SC insulin (group A)	CIPII (group B)	CIPII	SC insulin	Adjusted for treatment order *	*P*
Perceived hypoglycemia score	3.5 ± 2.1	3.0 ± 1.9	2.3 ± 1.6	3.8 ± 2.0	0.06	3.6 ± 2.5	2.6 ± 1.8				
End of treatment phase								2.4 ± 1.6	3.7 ± 2.2	−1.3 (−2.3, −0.3)	0.01
Change from baseline (%)								−25.3	+13.3		
Perceived hyperglycemia score	5.3 ± 0.9	4.8 ± 1.3	2.7 ± 1.5	4.6 ± 1.2	0.004	5.1 ± 1.3	2.5 ± 1.7				
End of treatment phase								2.6 ± 1.6	4.8 ± 1.3	−2.2 (−3.0, −1.5)	<0.01
Change from baseline (%)								−47.8†	−3.5		

Data are means ± SD, percentage mean change from baseline, or median (interquartile range). *Data for treatment effect are mean differences (95% CI) adjusted for treatment order assuming no carry over. † $P <$ 0.05 for change from baseline. SC, subcutaneous.

on guidelines (9). Drug costs for CSII were based on the Dutch national drug compendium (June 2007 prices), increased by the pharmacists' fee (€6.10) on the assumption of four prescriptions per year (excluding value-added tax [VAT]). Average daily insulin dose was based on trial data. For CIPII treatment, actual prices for both the intraperitoneal (IP) pump and insulin were used. Rates for rinse and refill procedures were based on the 2007 protocol and historical data instead of trial data. Life spans of 4 and 7 years were assumed for subcutaneous and CIPII pumps, respectively (10,11). Costs for self care and outpatient visits were considered to be equal for both therapy strategies and were therefore left out of the calculations.

The general linear model was used to test differences, taking treatment order into account (12). Tests for possible carry over were performed by comparing sequences. The McNemar test was used to compare paired proportions. Statistical analyses were performed with SPSS software.

RESULTS — Baseline and outcome of patients that completed the study (n = 23) are listed in Table 1 (a study flow chart is available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1758/DC1). Scores on most subscales of the SF-36 improved with CIPII compared with baseline. After one study period, all scores were higher with CIPII, although only statistically significant for the DTSQ and WHO-5 scores.

There were no significant differences between sequences (no carry over effects). When end point scores for CIPII and subcutaneous treatment were compared, the scores on all subscales were significantly higher with CIPII, with the exception of "social functioning" and "bodily pain."

With CIPII treatment, the number of patients scoring below 50 was half of that with subcutaneous treatment (6 vs. 13; P = 0.02). Furthermore, with CIPII, subjects perceived significantly less hypoglycemic and hyperglycemic events.

Costs are stated in detail in the online appendix. Direct pump- and procedure-associated costs for treatment with CIPII were estimated at €10,910 per year versus €4,810 for CSII. High costs of the IP pump (€20,000 at the time of the study) is largely responsible for the difference.

CONCLUSIONS — Treatment with CIPII improved HRQOL and treatment satisfaction in patients with type 1 diabetes who failed to reach satisfactory metabolic control with MDI and CSII, albeit against currently high costs.

Improvement of vitality and mental health on the SF-36 and a decline of problems in work and daily activities due to emotional problems indicate that CIPII, apart from physical improvement, improves mental components of health status as well, as confirmed by the results of the WHO-5 questionnaire. It is reassuring to find that, together with the beneficial effects of CIPII on HRQOL, CIPII treatment satisfaction is high and increased compared with subcutaneous treatment. Initiation of CIPII requires hospital admission and a surgical procedure to insert the pump, and could therefore be expected to have negative effects compared with treatment modalities not needing surgery. The improvement in glycemic control with less perceived complaints of hypo- and hyperglycemia probably compensates for this potential negative effect.

Annual costs of CIPII are about €6,000 higher than the annual costs of CSII at the moment, mainly because of the high price of the implantable pump and the insulin used in IP pumps. A formal cost-effectiveness analysis was beyond the scope of this study.

Nowadays many patients are able to achieve target levels with MDI or CSII. Still, a considerable proportion of type 1 diabetic patients are still not able to reach adequate control and satisfactory HRQOL despite all efforts. CIPII will then be a viable option, because it may improve A1C, HRQOL, and treatment satisfaction in selected patients.

A limitation of this study is that, because of the considerable increase in costs and scarcity of supplies, we did not enroll more patients. This might be the reason we were not able to show significant improvements after one study period. Although the interaction between treatment and period was not significant, we cannot completely rule out the existence of psychological carry over.

Based on our results, we conclude that CIPII has clear beneficial effects on HRQOL and satisfaction with treatment. CIPII should be considered as a treatment option, at least when satisfactory results of treatment are not reached with subcutaneous intensive insulin treatment regimens.

Acknowledgments— This study was supported by Medtronic Europe. The sponsor had no role in the study design, data collection, analysis, interpretation, or writing of the report.

No other potential conflicts of interest relevant to this article were reported.

Data from this manuscript were presented at the 44th annual meeting of the European Association for the Study of Diabetes in Rome, Italy, 7–11 September 2008.

We acknowledge E. van Ballegooie, who died in January 2008. He was part of the study group and was a pioneer concerning CIPII in the Netherlands since 1980. We thank W. van de Kolk for his help with cost calculations.

References

1. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, van Ballegooie E, Bilo HJ. Improved glycemic control with intraperitoneal versus subcutaneous insulin in type 1 diabetes: a randomized controlled trial. Diabetes Care 2009;32:1372–1377
2. Ware J, Snow K, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, The Health Institute, New England Medical Center, 1993
3. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, The Health Institute, New England Medical Center, 1994
4. World Health Organization, Regional Office for Europe. *Wellbeing measures in primary health care: the Depcare Project*. Report on a WHO Meeting, Stockholm, 1998
5. Bech P, Olsen LR, Kjoller M, Rasmussen NK. Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. Int J Methods Psychiatr Res 2003; 12:85–91
6. Löwe B, Spitzer RL, Gräfe K, Kroenke K, Quenter A, Zipfel S, Buchholz C, Witte S, Herzog W. Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. J Affect Disord 2004; 78:131–140
7. Bradley C. Diabetes treatment satisfaction questionnaire. In *Handbook of Psychology and Diabetes*. Bradley C. Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 111–132
8. Oostenbrink JB, Bouwmans CA, Koopmanschap MA, Rutten FF. *Manual for cost*: methods and standard costs for economic evaluations in health care. Amstelveen, the Netherlands, Health Care Insurance Board, 2004 [in Dutch]
9. Guidance on the use of continuous subcutaneous insulin infusion for diabetes: Technology Appraisal Guidance No. 57. National Institute for Clinical Excellence (NICE), 2003. Available from http://www.nice.nhs.uk. Accessed 26 August 2008
10. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess 2004;8:1–171
11. Haveman JW, Logtenberg SJ, Kleefstra N, Groenier KH, Bilo HJ, Blomme AM. Surgical aspects and complications of continuous intraperitoneal insulin infusion with an implantable pump. Langenbecks Arch Surg 2010;395:65–71
12. Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20