2019 Health Technology Reassessment Report

Systematic Reviews of the Safety, Effectiveness, and Cost-effectiveness of the Continuous Glucose Monitoring System and Insulin Pump for Type 1 Diabetes

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Summary

1. Continuous glucose monitoring system

Purposes

The continuous glucose monitoring system (CGMS) was first developed by Medtronic (Minneapolis, MN, USA) and approved by the US FDA in June 1999. CGMS is useful for treating diabetes patients with fluctuating glucose levels over a large range and frequent hypoglycemia. CGMS is aimed at efficient diabetes management and uses a sensor to measure changes in blood glucose levels in real-time. The device is used to continuously test the blood glucose level.

When type 1 diabetes patients purchase disposable products to self-monitor blood glucose using a prescription issued by a physician (an internist, pediatrician, or family medicine specialist) within 90 days at one of the medical equipment and supply stores registered with the Korea National Health Insurance Service, they receive insurance benefits.

Accordingly, to establish objective evidence to determine the clinical utility and financial value of CGMS based on its safety, effectiveness, and cost-effectiveness, the Korea National Health Insurance Service requested the Korea National Evidence-based Healthcare Collaborating Agency (NECA) to perform a systematic review (SR).

The NECA conducted this study with the following core question: “in comparison to self-monitoring of blood glucose (SMBG), is blood glucose management by CGMS safe, effective, and cost-effective in type 1 diabetes?"

Methods

Articles included in the assessment

The safety, effectiveness, and cost-effectiveness of CGMS were assessed by performing a qualitative SR. To assess safety and effectiveness, a literature search limited to SRs was performed, and 11 articles were selected. To assess cost-effectiveness, there was no article type restriction, and a total of 4 articles were selected.

Results

Safety outcomes

As reported in a previous study (Joo, et al., 2018), 2 of the selected articles, evaluated as "moderate-quality evidence," reported that complications and adverse events of CGMS were skin infection and allergic skin reaction, among others, in the area the sensor was attached. Accordingly, it was determined that although adverse skin reactions could occur, safety would not be a serious issue with CGMS because adverse events have rarely been reported, and they are mild.

Effectiveness outcomes

To assess the effectiveness of CGMS, the evaluation of HbA1c change, hyperglycemia, hypoglycemia, and quality of life, out of the indices used in the previous study (Joo et al., 2018), was performed. Joo et al. (2018), in a study involving pediatric patients with type 1 diabetes, reported that CGMS, compared with SMBG, showed a statistically significant reduction in HbA1c in all 6 articles evaluated as "high-quality evidence;" in 5 articles evaluated as "moderate-quality evidence," HbA1c was reduced although the change was not statistically significant in most of the studies. Based on the finding that CGMS facilitated an equivalent or greater HbA1c reduction than SMBG, Joo et al. (2018) concluded that CGMS was

effective. Accordingly, it is concluded in this study that CGMS is effective, given that it showed an equivalent or greater effect, compared with SMBG, in reducing HbA1c in both pediatric and adult type 1 diabetes patients.

The frequency, timing, and risk ratio of hypoglycemia were also examined. Similar to the study by Joo et al. (2018), this study determined that evidence was insufficient to conclude that the use of CGMS reduces the incidence of hypoglycemia in pediatric or adult patients.

To examine the quality of life following the use of CGMS, the findings of 5 original articles included in 2 "high-quality evidence" SR articles were summarized. Based on 2 studies reporting significant differences, Langendam et al. (2012) interpreted that the significant difference was attributable to the increased satisfaction due to the combined use of an insulin pump and CGM as the patients had not used an insulin pump before participating in the study. Accordingly, the current study, similar to Joo et al. (2018), determined that evidence was insufficient to conclude that the use of CGMS increases the quality of life in pediatric or adult patients in comparison with SMBG. However, in the DIaMonD (2017), a clinical trial recently conducted to evaluate the quality of life in type 1 adult patients, the confidence related to hypoglycemia increased, stress reduced, and wellbeing, the health status, and the fear for hypoglycemia improved. In particular, it helped reduce severe hypoglycemic events during sleep or driving. Thus, the quality of life issue needs to be reevaluated in additional studies.

Cost-effectiveness outcomes

Of the 4 articles selected for cost-effectiveness analysis, 2 were conducted in the US, 1 in Canada, and 1 in Spain. Regarding the analytic point of view, 3 of the articles used the social perspective, and 1 used the payer perspective. The articles that used the social perspective (McQueen et al., 2011; Chaugule et al., 2017; Wan et al., 2018) assessed CGMS as a cost-effective alternative, and the one article that used the payer perspective (Garcia-Lorenzo et al., 2018) assessed it as not cost-effective. The ICER thresholds were $45,033 (USD), $33,789 (CAD), and $33,459 (USD) for the 3 articles that concluded that CGMS was cost-effective, respectively, and €880,229/QALY for the article that concluded that it was not cost-effective. The Spanish study (Garcia-Lorenzo et al., 2018), which concluded that CGMS was not

cost-effective from a social perspective, used the utility values of diseases instead of diabetes as a disutility in the utility estimation. Jesus (2019) raised several issues with the Spanish study (that is, recent articles were not included, the costs of ER visits and hospital admissions due to hypoglycemia and ketoacidosis were not factored in, and the most recent devices were not considered) and pointed out that the estimated ICER threshold was too low, suggesting that it could be a cost-effective alternative. Hence, in Korea, to determine cost-effectiveness, policy decisions should be made with considerations of the domestic situation.

Conclusion and suggestions

Considering the 11 articles included in the effectiveness assessment, it seems that the clinical safety and effectiveness of CGMS are equivalent or superior to those of SMBG for adult type 1 diabetes patients, as reported by Joo et al. (2018). However, allergic skin reactions are likely to occur, and the continuous attachment of the CGMS sensor to the skin should be considered. Concerning effectiveness, although the magnitude of the HbA1c reduction was 0.1–0.5%, it is difficult to conclude on the decrease in the incidence of hypoglycemia and hyperglycemia, the maintenance of glucose level, impact on treatment outcome, and quality of life with the use of CGMS based on existing evidence.

In addition, a few other articles (Wojciechowski et al., 2011; Poolsup et al, 2013) described the additional benefits of real-time CGMS, such as the decreased incidence of hypoglycemic episodes, self-monitoring as a lifestyle, and the feasibility to use it as a device supporting both pharmacological and lifestyle interventions. It is found in the literature that the extent of usage of the sensor was related to glucose management, and the sensor may be effective for managing glucose levels in pediatric patients with the help of parents. Thus, CGMS could be more effective in controlling blood glucose in pediatric type 1 diabetes patients if the patients and their parents are carefully trained on the use of the sensor.

Recent articles have reported the convenience of CGMS as a lifestyle intervention, as well as its effect on hypoglycemia, its improvement of the quality of life, and the usage level-dependent effect. Accordingly, policymakers need to consider patient convenience. Currently, CGMS is continually advancing. Hence, a policy direction

would be to encourage maximal patient convenience by recommending a device design that will facilitate intermittent monitoring of glucose levels to minimize the discomfort in wearing while reducing the cost of sensors.

This review of SRs was conducted over a short period to aid in policy decisions. Thus, the study has the following limitations, and caution should be taken in interpreting the results. The main limitations are as follows. Because the article type was limited to a systematic review, as in the previous study (Joo et al., 2018), (1) some of the articles were used in two or more SRs, (2) the results should be interpreted with care as the statistical effect of the overlapping articles could be over-interpreted, and (3) the synthesis of the results reported in the original articles should be performed separately. However, regarding the synthesis of the study findings, it was difficult to make conclusions only based on the original articles included in the selected SRs because they were highly heterogeneous. Accordingly, future research to establish evidence should be conducted based on original articles that will be conducted in the future to investigate quality of life issues, such as hyperglycemia and hypoglycemia (including nocturnal hypoglycemia), and cost-effectiveness.

2. Insulin pump

Purposes

Continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, is a medical device developed to administer insulin continuously for 24 hours. CSII helps to regulate and maintain the blood glucose level close to normal by maintaining blood insulin levels close to the natural levels for the human body.

Currently, the Korea National Health Insurance Service is considering expanding the health insurance benefits to cover convenient medical devices for glucose monitoring in relation to the effort to establish protective measures for pediatric diabetes patients. Considering the demand for health insurance benefit expansion and timeliness, disposable products (sensors) necessary for the use of CGMS were given the priority and started being covered on January 1, 2019 (the Office for Government Policy Coordination, 2017). However, CGMS and CSII, which are expensive and currently not covered by the national health insurance, are still under review for insurance coverage.

Accordingly, to establish objective evidence for the clinical utility and economic value of CSII based on its safety, effectiveness, and cost-effectiveness, the Korea National Health Insurance Service requested the Korea National Evidence-based Healthcare Collaborating Agency (NECA) to perform a systematic review (SR).

In this study, the NECA aimed to assess the safety, effectiveness, and cost-effectiveness of CSII in type 1 diabetes patients by comparing it with multiple daily insulin injections (MDIs), which is the conventional treatment.

Methods

Articles included in the assessment

The safety, effectiveness, and cost-effectiveness of CSII were assessed by performing an SR. For the assessment of safety and effectiveness, the article type was limited to an SR, and 17 SR articles were selected. For the assessment of cost-effectiveness, the article type was not restricted. Seventeen articles were selected, of which 4 were SRs, 4 were randomized clinical trials, 1 was a pilot study, and 8 were categorized as others such as simulation and hypothesis-testing. Five of the 17 articles were health technology assessment (HTA) reports.

Outcome indices

The safety of CSII was primarily assessed with such indices as severe hypoglycemia, nocturnal hypoglycemia, and diabetic ketoacidosis (DKA). Additionally, any results reported in the articles regarding non-severe mild/moderate hypoglycemia, hyperglycemia, and adverse effects associated with CSII (like insulin injection site problem and problems with the insulin pump device), including severe adverse events such as death, were also included.

The primary outcome index used in the effectiveness assessment was a change in HbA1c. Any reports in the articles regarding blood glucose levels before or after a meal were also presented in the Data Extraction section. The results were presented separately for each of the 3 patient groups (pediatrics, adults, and pregnant women).

Cost-effectiveness was examined using economic indicators such as ICER, QALY, and DALY as primary outcome measures. Of the 17 articles selected for cost-effectiveness assessment, one (Colquitt et al., 2004) was excluded from analysis because the cost-effectiveness assessment results were not reported.

Overview of the article selection process and analysis

For this SR, a literature search was performed using 5 domestic databases (KoreaMed, RSISS, KISS, NDSL, and KMBASE) and 3 foreign databases (Ovid-MEDLINE, Ovid-EMBASE, and Cochrane Library).

The assessment of safety, effectiveness, and cost-effectiveness was independently performed by 2 researchers. Disagreements were resolved by the two researchers through a discussion based on the original article or through a review by a subcommittee.

A total of 456 articles on safety and effectiveness assessment were extracted from the domestic and foreign databases (143 domestic and 313 foreign articles). The duplicates (65 domestic and 54 foreign) were excluded, and the title, abstract, and full-text of the remaining articles (78 domestic and 259 foreign) were examined. Three hundred and twenty articles (78 domestic and 242 foreign) were excluded based on the selection/exclusion criteria. Finally, 17 articles (all foreign articles) were selected for the safety and effectiveness assessment. The list of the 17 finally selected articles is presented in the appendix.

Regarding cost-effectiveness, 1,865 articles (all foreign articles) were obtained from the literature search using the domestic and foreign databases. Of those, 314 duplicates were excluded, and the title, abstract, and full-text of the remaining 1,551 articles were examined. A total of 1,534 articles were excluded based on the selection/exclusion criteria, and 17 articles were finally selected to assess cost-effectiveness.

Results

A literature search using domestic and foreign databases showed no domestic articles comparing the safety, effectiveness, and cost-effectiveness of CSII and MDI.

Safety outcomes

Sixteen out of the 17 articles presented severe hypoglycemia as the primary outcome measure, and 2 articles presented nocturnal hypoglycemia. Regarding the

incidence of hypoglycemia (including severe hypoglycemia and nocturnal hypoglycemia), it was determined that there was no significant difference between CSII and MDI patient groups in pediatric or adult patients. Regarding the incidence of hypoglycemia in pregnant women (including severe hypoglycemia and nocturnal hypoglycemia), it was difficult to determine the significance of the inter-group difference based on only 2; however, the difference seemed not to be significant.

A total of 6 articles, including 2 articles focusing only on pregnant women, reported DKA. Based on a review of the 6 articles, it was determined that CSII and MDI patient groups did not show a significant difference in any of the pediatric, adult, and pregnant patient groups.

Additionally, 4 articles reported that the difference between the MDI and CSII patient groups was not significant based on the patterns of non-severe mild/moderate hypoglycemia.

Only 1 article (Yeh et al., 2012) reported the outcome of hyperglycemia. It was an SR performed by classifying the therapeutic interventions and comparators into 3 groups (CSII vs. MDI; CGM vs. SMBG; sensor-augmented pump, SAP vs. MDI+SMBG) in pediatric and adult patients. Two studies included in the article (Bergenstal et al., 2010; Hermanides et al., 2011) reported that the duration of hyperglycemia was significantly shorter in SAP than in MDI ($p < 0.001$).

The adverse events associated with the use of CSII (like insulin injection site problem and issues with insulin pump devices) were reported in 1 article (Jeitler et al., 2008). One (Nosadini et al., 1988) of the 23 RCT articles included in that article reported one case of death in the CSII patient group. The patient was reported to have had hypertension, fever, and ketonuria 2 days before death and there was no change in the glucose level although the insulin infusion dose was increased. Two articles reported infusion site problems (Hoogma et al., 2006; Schottenfeld-Naor et al., 1985). Specifically, the infusion site problems reported in Schottenfeld-Naor et al. (1985) were catheter problems, pump arrest or dosage errors, battery problems, and syringe dislocation. Additionally, 2 articles reported other adverse events without providing details (Hoogma et al., 2006; Ziegler et al., 1990).

Effectiveness outcomes

All of the 17 articles reported a change in HbA1c as the primary outcome measure. In 13 of the articles, HbA1c significantly decreased in the patients treated with CSII (therapeutic intervention) compared with MDI (comparator). Based on the results of the 13 articles, CSII (therapeutic intervention) significantly reduced HbA1c compared with MDI (comparator) in pediatric as well as adult patients. On the other hand, only 2 articles reported results in pregnant women, and changes in HbA1c were reported although they varied depending on the trimester (first, second, and third) of the patients. Hence, it was difficult to determine the significance of the inter-group difference.

Cost-effectiveness outcomes

From the short-term perspective, CSII may be considered as not cost-effective. However, it can be thought to be cost-effective from a long-term perspective, as shown in 3 articles (Roze et al., 2015; Cohen et al., 2007; Roze et al., 2005), because it is expected that the decrease in the incidence of diabetic compilations by controlling and maintaining the glucose levels close to normal has an effect of reducing treatment cost.

Education-related outcomes

Education-related outcomes (including how to use insulin pumps) were reported in 8 articles; 4 were selected for the safety and effectiveness assessment whereas the other 4 were selected for the cost-effectiveness assessment. All of the articles indicated if there was a diabetes-related practice or education, but none performed significance testing on the difference between the therapeutic intervention and comparator.

Of the articles selected for cost-effectiveness assessment, Heller et al. (2017) reported that there was an improvement in diabetes control in CSII and MDI groups alike and suggested that the extensive use of CSII before systematic training may not improve diabetes management or be cost-effective. Pollard et al. (2018) reported that NHS medical staff should provide patients with systematic training proven for benefits before considering prescribing CSII for type 1 diabetes, unless there are

clinical reasons for them to use it right away. Accordingly, the use of CSII accompanied by proactive and ongoing practice or training is expected to improve the glucose level and be cost-effective from a long-term perspective.

Evaluated categories and limitations

During the literature search using domestic and foreign databases, no domestic articles compared CSII and MDI based on safety, effectiveness, and cost-effectiveness.

The CSII device was limited to those products currently imported and approved for sale in Korea, and the literature search was performed using the PICO strategy, as described in the Study Design section. Accordingly, studies on artificial pancreas systems equipped with the internal function of automatic insulin infusion (for example, MiniMed 670G) were excluded from the SR.

CSII is an expensive medical device, and the user's knowledge about the device and skill level are important variables. Hence, the importance of training (including how to use the pump) in diabetes management was stressed several times during subcommittee meetings. Therefore, the current SR study too presented the study findings related to diabetes education in association with CSII and MDI that were reported in the selected articles.

If an article revealed the CSII product name, it was also presented in the Data Extraction section. However, the main purpose of this study was to review the safety, effectiveness, and cost-effectiveness of CSII and MDI in type 1 diabetes patients, and not to compare various CSII devices based on function and specification. Thus, the results were for the CSII and SAP groups, and individual CSII products were not evaluated.

Conclusion and Suggestions

It is difficult to say that treatment with CSII is cost-effective in the short-term because of the costs of the device and the related disposable products necessary for using the device. However, based on the results reported in the SR articles selected in this study, it seems of great significance that practice or training on how to use

CSII is a must. The findings show that the decrease in HbA1c (%), an important outcome of glucose management, was significant in the treatment with CSII and MDI. Through continuous and stable glucose management, the occurrence of chronic complications of diabetes (such as retinopathy, nephropathy, neuropathy, and cardiovascular disease) are likely to be prevented or delayed, which will have an effect of reducing the frequency of healthcare use due to the decreased frequency of complication-related problems. Hospital admissions or outpatient visits of diabetes patients will also decrease. Accordingly, over the long-term, it is expected that healthcare spending will decrease.