2019 Health Technology Reassessment Report

Safety and Effectiveness Assessment of Ab interno Trabeculotomy with High Frequency Current

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Abstract (English)

□ Assessment background

Ab-interno trabeculotomy (AIT) with high-frequency current is a procedure used to selectively remove on the trabecula and inner wall of Schlemm's canal in patients with glaucoma to preserve as much as possible the normal outflow tract, from the outer wall of Schlemm's canal, collector channel, to aqueous vein. This technology received new health technology assessment in 2011 and 2013 and was subsequently classified as registered non-coverage item on April 20, 2015 (Ministry of Health and Welfare notification 2015-59).

As a part of the project to reassess preliminary coverage implementation items (NR19-001 health technology reassessment project, Principal investigator: In-Soon Choi), AIT with high-frequency current, which is currently classified as a registered non-coverage item among the items assessed in previous new health technology assessments, was updated with the latest evidence.

□ Committee operation

A subcommittee consisting of five members held a total of three subcommittee sessions over a 3-month period between April 26 and July 24, 2019 to discuss and reach conclusions on PICO-TS, article selection, and data synthesis of the systematic literature review and assessment of level of evidence.

In 2019 (September 20, 2019), the research planning and management committee conducted a final review of the findings in the assessment of clinical safety and effectiveness of AIT with high-frequency current.

□ Assessment objectives and methods

A systematic literature review was performed on AIT with high-frequency current, which is currently classified as a registered non-coverage item, to establish the medical evidence needed for setting a reasonable coverage standard. This assessment was designed to review the study results reported in additional articles published since the previous assessment. In accordance with the methodology for a systematic literature review, articles published between 2013 (one year prior to the previous assessment) and April 2019 were searched and those articles were reviewed together with the articles that were included in the assessments in 2011 and 2013.

The safety and effectiveness of AIT with high-frequency current in patients with glaucoma were assessed based on the following indicators: procedure-related complications and adverse events [anterior chamber bleeding, increased intraocular pressure (IOP), endophthalmitis, re-operation, visual decline, choroidal damage, persistent ocular hypotony, aqueous outflow, malignant glaucoma, and shallow anterior chamber), decrease in IOP, change in the amount of anti-glaucoma drug used, and procedure success rate. Procedure success rate followed the definition given by the Tube versus Trabeculectomy (TVT) Study Group – mean postoperative IOP of $\leq$ 21 mmHg and being $\geq$ 20% lower than the baseline value during at least two consecutive follow-ups after at least three months after the procedure, while also not requiring a secondary procedure. Cases that did not need additional drug therapy and the procedure did not fail according to the definition were classified as complete success, whereas cases that needed additional drug therapy were classified as qualified success.

Risk of bias assessment was performed using Cochrane's risk of bias for randomized clinical trials (RCTs) and risk of bias for nonrandomized studies (ROBANS) ver 2.0 for non-RCTs. The major findings in the articles that were

ultimately selected were assessed for level of evidence using GRADEpro according to the grading of recommendations assessment development and evaluation (GRADE) method.

□ Assessment results

A total of 11 articles were ultimately selected, including one RCT and 10 non-RCTs. Because the control groups varied, the results were presented with the control groups classified as the trabeculectomy (one RCT and four non-RCTs), iStent (four non-RCTs), glaucoma drainage device implantation (two non-RCTs), and other (both groups receiving Ahmed glaucoma valve implantation but only the intervention group receiving additional AIT with high-frequency current; one non-RCT) based on subcommittee discussions.

1. Safety

The safety of AIT with high-frequency current was examined by the incidence of anterior chamber bleeding, increase in IOP, endophthalmitis, re-operation, visual decline, choroidal damage, persistent ocular hypotony, aqueous outflow, malignant glaucoma, and shallow anterior chamber by each control group.

Postoperative anterior chamber bleeding in trabeculectomy control group was reported in one RCT and one non-RCT. One RCT reported incidence of 40% in the intervention group and 0% in the control group, but the difference between the two groups was not significant (p-value=0.60). One non-RCT reported incidence of 100% in the intervention group and 2.9% in the control group, but the symptoms were localized and disappeared within 1-7 days without any specific treatment. Postoperative anterior chamber bleeding in iStent control group was reported in two RCTs. Both RCTs reported significantly higher

incidences in the intervention group and that the symptoms disappeared after one week or one month. Each study reported that anterior chamber bleeding could be attributed to the characteristics of the procedural method, explaining that anterior chamber bleeding is a common symptoms because blood backflow could occur easily due to AIT with high-frequency current creating a gap between the trabecula and the inner wall of Schlemm's canal.

Postoperative increase in IOP (> 10 mmHg) in trabeculectomy control group was reported in one non-RCT, occurring in both the intervention group (3.5%) and the control group (2.9%). Postoperative increase in IOP in iStent control group was reported in two non-RCTs. One study reported incidence of 33% in the intervention group and 16% in the control group, but the difference between the two groups was not significant (p-value=0.07). The other study reported incidence of 2.8% in the intervention group and 0% in the control group. Although a significant difference between the two groups was found, most of the symptoms disappeared by postoperative one-month. Meta-analysis of two non-RCTs showed a significant difference between the two groups (OR 2.52, 95% CI 1.01~6.30, I^2=0%).

Postoperative endophthalmitis was reported in only one non-RCT with iStent control group, with no incidence of postoperative endophthalmitis in both the intervention and control groups.

Glaucoma re-operation in trabeculectomy control group was reported in one RCT and two non-RCTs. One RCT reported glaucoma re-operation rate of 10% in the intervention group and 0% in the control group, but the difference between the two groups was not significant (p-value=0.36). In two non-RCTs, meta-analysis results showed no significant difference between the two groups. Re-operation in iStent control group was reported in three non-RCTs, with no

significant difference between the two groups. Re-operation in glaucoma drainage device implantation control group was reported in two non-RCTs and the meta-analysis results showed no significant difference between the two groups.

Postoperative visual decline with ≥2 Snellen lines in trabeculectomy control group was reported in one non-RCT with no incidence in both groups. Postoperative visual decline in glaucoma drainage device implantation control group was reported in one non-RCT, with incidence of 0% in the intervention group and 3.1% in the control group.

Postoperative choroidal damage (choroidal detachment, effusion) in trabeculectomy control group was reported in one RCT and two non-RCTs. One RCT reported incidence of 0% in the intervention group and 22.2% in the control group. Two non-RCTs reported incidences in only the control group (9% and 3.9% each), but none in the intervention group. The meta-analysis results confirmed a significant difference between the two groups. Postoperative choroidal damage in iStent control group was reported in two non-RCTs, with no incidence in both groups. Postoperative choroidal damage in glaucoma drainage device implantation control group was reported in one non-RCT, with incidence of 0% in the intervention group and 9.3% in the control group.

Postoperative persistent ocular hypotony in trabeculectomy control group was reported with three non-RCTs. All three studies incidences in only the control group (17%, 8.3%, and 4.9% each), but none in the intervention group. The meta-analysis results confirmed a significant difference between the two groups (OR 0.06, 95% CI 0.01~0.35, I^2=0%). Persistent ocular hypotony in iStent control group was reported in one non-RCT, with no incidence in both groups. Persistent ocular hypotony in glaucoma drainage device implantation control

group was reported in one non-RCT, with incidence of 0% in the intervention group and 6.9% in the control group.

Postoperative aqueous outflow in trabeculectomy control group was reported in one RCT and two non-RCTs. One RCT reported incidence of aqueous outflow of 0% in the intervention group and 22.2% in the control group. One non-RCT reported no incidence of aqueous outflow in both groups, whereas the other study reported incidence of 0% in the intervention group and 11.8% in the control group.

Postoperative malignant glaucoma in trabeculectomy control group was reported in one non-RCT, with incidence of 0% in the intervention group and 4.3% in the control group. Postoperative malignant glaucoma in glaucoma drainage device implantation control group was reported in one non-RCT, with incidence of 0% in the intervention group and 3.4% in the control group.

Postoperative shallow anterior chamber in trabeculectomy control group was reported in one non-RCT, with incidence of 0% in the intervention group and 7.8% in the control group.

2. Effectiveness

The effectiveness of AIT with high-frequency current was examined by decrease in IOP, change in the amount of anti-glaucoma drug used, and procedure success rate by each control group.

Mean postoperative IOP in trabeculectomy control group was reported in one RCT and four non-RCTs. One RCT reported that the mean IOP was ultimately lower in the intervention group than in the control group, but the difference was not significant and both groups showed similar level of decrease in IOP. Meta-analysis of four non-RCTs showed that the final mean postoperative IOP was

significantly higher in the intervention group than in the control group (WMD 5.26 mmHg, 95% CI 3.83~6.68, I^2=0.0%). Meta-analysis of four non-RCTs with iStent control group showed significantly higher final mean postoperative IOP in the intervention group than in the control group (WMD 2.12 mmHg, 95% CI 1.15~3.09, I^2=7.6%). Meta-analysis of two non-RCTs with glaucoma drainage device implantation control group showed no significant difference in final mean postoperative IOP between the two groups. One non-RCT with "other" control group ((both groups receiving Ahmed glaucoma valve implantation but only the intervention group receiving additional AIT with high-frequency current) reported that the final mean postoperative IOP was significantly lower in the intervention group than in the control group.

Mean postoperative amount of anti-glaucoma drug used in trabeculectomy control group was reported in one RCT and four non-RCTs. One RCT reported that the mean amount of anti-glaucoma drug used ultimately decreased more in the intervention group than in the control group, but the difference between the two groups was not significant. Meta-analysis on three out of four non-RCTs that could be analyzed showed that the mean postoperative amount of anti-glaucoma drug used was significantly higher in the intervention group than in the control group (WMD 1.59개, 95% CI 1.18~2.01, I^2=0.0%). Mean postoperative amount of anti-glaucoma drug used in iStent control group was reported in three non-RCTs and meta-analysis of these studies showed no significant difference between the intervention and control groups. Mean postoperative amount of anti-glaucoma drug used in glaucoma drainage device implantation control group was reported in two non-RCTs and meta-analysis of these studies showed that the mean postoperative amount of anti-glaucoma drug used was significantly lower in the intervention group than in the control group

(WMD -1.04개, 95% CI –1.55~-0.53, I^2=0.0%). One non-RCT with “other” control group (both groups receiving Ahmed glaucoma valve implantation but only the intervention group receiving additional AIT with high-frequency current) also showed that the mean postoperative amount of anti-glaucoma drug used was significantly lower in the intervention group than in the control group (p-value=0.001).

Procedure success rate in trabeculectomy control group was reported in one RCT and three non-RCTs. One RCT reported complete success rate of 20% in the intervention group and 50% in the control group, with no significant difference between the two groups. Qualified success rate was 20% in the intervention group and 37.5% in the control group, with no significant difference between the two groups. Three non-RCTs did not report on complete success rate. Meta-analysis of qualified success showed that qualified success rate was significantly higher in the control group than in the intervention group, but heterogeneity was high (OR 0.55, 95% CI 0.39~0.78, I^2=82.5%). Complete and qualified success rates in iStent control group was reported in one non-RCT each. Complete success rate was 18.2% in the intervention group and 9.7% in the control group, but the difference between the two groups was not significant. Qualified success rate was 34.6% in the intervention group and 59.2% in the control group, with a significant difference between the two groups (p-value=0.01). No study reported on completed success rate in glaucoma drainage device implantation control group, while qualified success rate was reported in two non-RCTs. Meta-analysis of these two non-RCTs showed no significant difference between the intervention and control groups. One non-RCT with “other” control group (both groups receiving Ahmed glaucoma valve implantation but only the intervention group receiving additional AIT with high-

frequency current) reported complete success rate of 56.2% in the intervention group and 13.5% in the control group and qualified success rate of 70% in the intervention group and 65% in the control group, but the differences between the two groups were not significant.

3. Level of evidence assessment

Level of evidence assessment results showed moderate for all indicators in one RCT and low or very low for all indicators by control groups in 10 non-RCTs.

□ Conclusions

The subcommittee on AIT with high-frequency current opined that, with respect to safety, anterior chamber bleeding, which was reported to be a complication associated with the intervention, could be attributed to the characteristics of the procedural method that creates an aqueous outflow pathway by perforating a specific, narrow area and that anterior chamber bleeding and increase in IOP could not be viewed as significant complications or adverse events since most are early complications that heal naturally within few days. Besides this, incidences of endophthalmitis, re-operation, visual decline, choroidal damage, persistent ocular hypotony, aqueous outflow, malignant glaucoma, and shallow anterior chamber showed no significant differences when compared by type of control group (trabeculectomy, iStent, glaucoma drainage device implantation, and other) or incidences were higher in the control group. Accordingly, AIT with high-frequency current was determined to be safe.

The subcommittee also opined that the effectiveness of AIT with high-frequency current could be recognized since all studies confirmed decrease in

IOP (mean decrease of 29.9%) and amount of anti-glaucoma drug used (mean decrease of 37.2%) after the intervention, as compared to before the intervention. Moreover, because glaucoma is a disease with diverse patient conditions that requires long-term care, this procedure may be considered before opting for other highly invasive procedures. However, because this procedure selectively removes only the trabecula and inner wall of Schlemm's canal, it would be inappropriate for cases involving closed-angle glaucoma, neovascular glaucoma, and tumor-induced secondary glaucoma that are difficult to approach with the equipment. Except for such cases, this procedure was determined to be appropriate for patients with glaucoma.

Accordingly, the subcommittee on AIT with high-frequency current proposed the following based on currently available assessment results.

AIT with high-frequency current was assessed to be a technology with evidence of safety and effectiveness for use on patients with glaucoma, except in cases involving closed-angle glaucoma, neovascular glaucoma, and tumor-induced secondary glaucoma that are difficult to approach with the equipment, based on it being less invasive than conventional filtration surgery and having fewer complications, while enabling effective regulation of IOP.

The Health Technology Reassessment Committee reviewed and determined that the findings of the subcommittee on AIT with high-frequency current are valid (September 20, 2019).