NECA-Health Technology Reassessment Project

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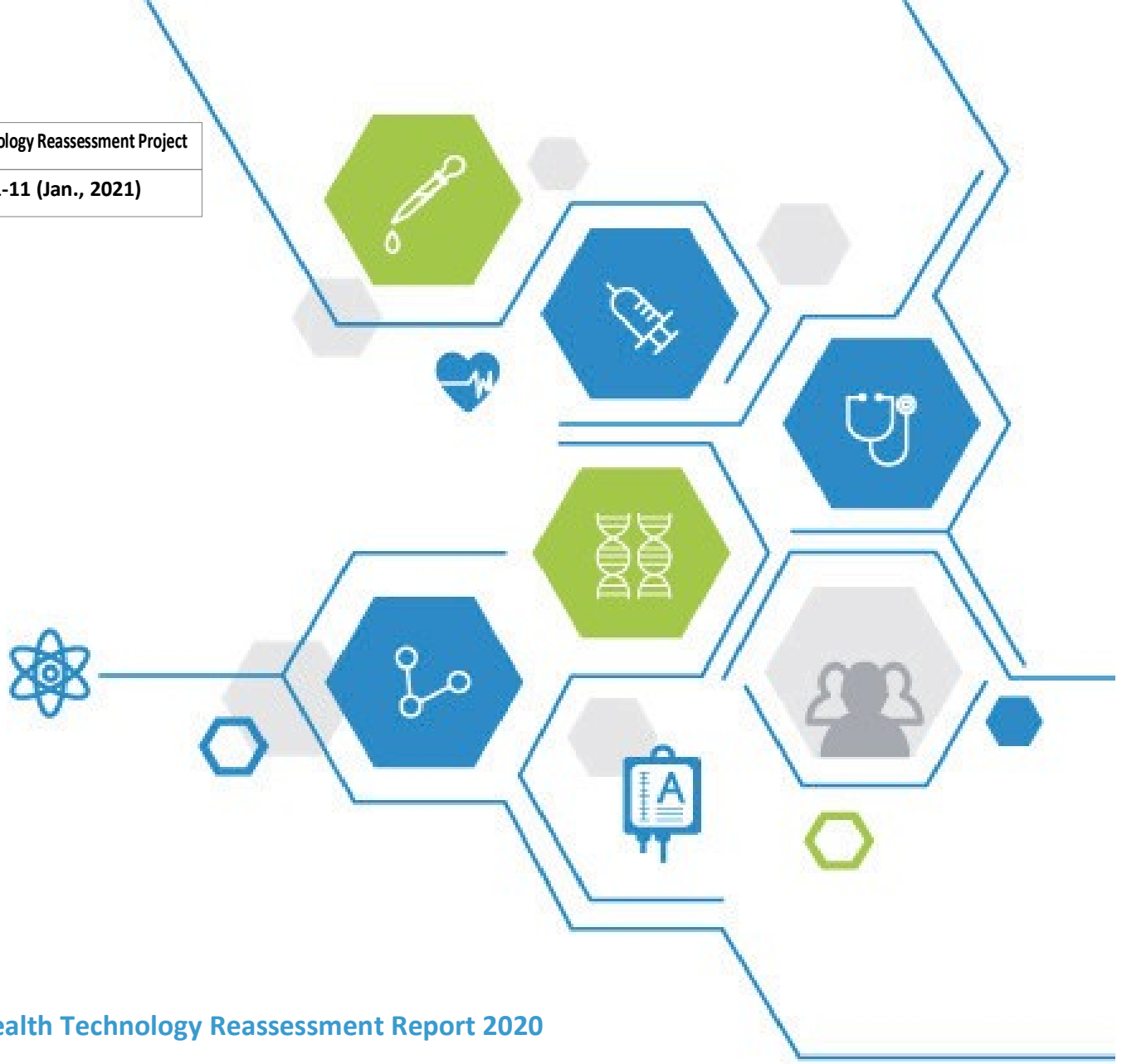

Health Technology Reassessment Report 2020

Autologous Bone Marrow Stem Cell Treatment

- in patient with Critical Limb Ischemia -

Injection of Centrifuged Bone Marrow at Ischemic Area

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Summary Statement

Background

The concerned technology, Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area, is used to delay foot amputation in patient with Fontaine's Stage III or IV occlusive peripheral arterial disease or severe critical limb ischemia or treat the same diseases.

With its safety and effectiveness announced as a result of New Health Technology Assessment in 2012, the technology was publicly announced (by the Ministry of Health and Welfare as Public Announcement #2014-204, Nov. 27, 2015) as a new technology as a non-benefit item. Becoming subject to reassessment in the internal monitoring process as part of Health Technology Reassessment Project 2020, the technology was brought to the 2nd meeting of Health Technology Reassessment Committee in 2020 (Feb. 14, 2020), followed by the safety and effectiveness review in the competent sub-committee comprised of 8 different specialists (1 vascular surgeon, 1 thoracic surgeon, 2 cardiovascular physicians, 2 radiologists, 1 orthopedic surgeon, 1 evidence-based medicine specialist) by way of systematic literature review(SLR), and the final screening for conclusion in the 1st Health Technology Reassessment Committee in 2021 (Jan. 15, 2021).

Methodology

Review of the relevant clinical therapeutic guidelines and systematic literature review(SLR) was conducted for assessment of safety and effectiveness of the technology. Taking into account the study's purpose, all methodologies were screened by the sub-committee in charge of assessing Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area (the "sub-committee") into confirmation.

In this study, relevant clinical therapeutic guidelines mean clinical therapeutic guidelines announced by the local and international academic society and institutions. These guidelines were searched out for review. Three different international literature databases and five different domestic literature databases were referred to in selection of literatures to be reviewed in systematic literature review(SLR). This review, as well as data extraction and risk of bias assessment, was conducted under literature inclusion and exclusion criteria and by two separate reviewers. The synthesizable types of data were meta-analyzed. Cochrane's Risk of Bias Tool was used for risk of bias assessment. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to present evidence for making clinical practice recommendations. The final screening for conclusion of result and grading of the technology taking into account the sub-committee's opinion was held in the Health Technology Reassessment Committee.

Result

In this study, two clinical therapeutic guidelines and 7 literatures for SLR were selected for assessment.

According to the clinical therapeutic guideline published jointly by European Society of Cardiology(ESC) and European Society of Vascular Surgery(ESVS) in 2017, angiogenic gene and stem cell therapy in chronic(critical) limb-threatening ischemia(CLTI) patient has less than enough evidence and needs more researches to be done and is graded Recommendation Grade III (not recommended) and Evidence Level B (data derived from single randomized clinical trial or multiple nonrandomized clinical trials). According to the clinical therapeutic guideline on CLTI published jointly by The Society for Vascular Surgery(SVS), European Society of Vascular Surgery(ESVS) and World Federation of Vascular Societies(WFVS) in 2019, the technology needs additional Phase 3 studies to verify effectiveness of gene therapy and cell therapy and is considered as an 'investigational' technology until backed by further evidences by grading the technology as, when used for the restrictive purpose of treating angiogenesis in the registered subjects being CLTI patients, Recommendation Grade 1 (Strong) and Evidence Level B (Moderate).

Safety was assessed by way of SLR, using 'Adverse Event' and 'Death' as viable indices.

According to meta analysis of a total of 7 literatures where at least 1 adverse event was reported, 73 out of 241 Study Group subjects (30.3%) and 51 out of 203 Control Group subjects (25.1%) were reported to manifest adverse event, with no statistically significant inter-Group difference (RR 0.98, 95% CI 0.86, 1.11). Reported adverse events were leukemia, inguinal hematoma, fever, cerebral stroke, edema, leg pain, skin ulcer and focal inflammation. Out of those, adverse events from only 2 literatures (Teraa et al, 2015b; Powell et al, 2011) were reported to be related to surgical interventions taken. According to meta analysis of a total of 6 literatures reporting death, 13 out of 213 Study Group subjects (6.1%) and 14 out of 177 Control Group subjects (7.9%) were reported dead, with no statistically significant inter-Group difference (RR 0.85, 95% CI 0.42, 1.73). Despite 2 literatures (Li et al, 2013; Powell et al, 2011) reporting possible relationship between death and surgical interventions taken, it was determined the dead cases were not directly related to surgical interventions taken.

Meanwhile, effectiveness of the technology was assessed, by way of SLR, using such indices as major foot amputation, minor foot amputation, amputation-free survival, improvement of ulcer healing, increase in Ankle-Brachial pressure Index(ABI), increase in transcutaneous oxygen pressure($TcPO_2$), changes in pain, ambulatory indices and quality of life indices.

According to meta analysis of a total of 7 literatures reporting major foot amputation, no statistically significant inter-Group difference between Study Group and Control (Placebo) Group was observed (RR 0.81, 95% CI 0.54, 1.23). According to meta analysis of a total of 2 literatures reporting minor foot amputation, no statistically significant inter-Group difference between Study Group and Control (Placebo) Group was observed (RR 1.02, 95% CI 0.46, 2.24). According to meta analysis of a literature reporting amputation-free survival, statistically significant inter-Group difference between Study Group and Control (Placebo) Group was observed (p=0.0376). According to meta analysis of a total of 2 literatures reporting continuous index of change in ulcer size and another 2 literatures reporting binary data of the percentage of subjects with improvement of ulcer healing, no statistically significant inter-Group difference was observed. According to meta analysis of 5 out of 7 literatures reporting increase in Ankle-Brachial pressure Index(ABI) - the meta-analyzed 5 literatures reported ABI as continuous variable, in 3 out of those 5 literatures with synthesizable data, no statistically significant inter-Group difference was observed (MD 0.03, 95% CI -0.03, 0.08). According to meta analysis of a total of 3 literatures reporting binary data of the percentage of subjects with increase in ABI, no statistically significant inter-Group difference between Study Group and Control (Placebo) Group was observed (RR 4.37, 95% CI 0.80, 23.97). According to meta analysis of 2 out of 3 literatures with synthesizable data, no statistically significant inter-Group difference was observed (RR 0.97, 95% CI 0.54, 1.72). According to meta analysis of 4 literatures reporting changes in pain as continuous index, another 4 literatures

reporting increase in transcutaneous oxygen pressure($TcPO_2$), 1 literature reporting ambulatory indices, and 3 literatures reporting quality of life indices, no statistically significant inter-Group difference was observed.

Conclusion and Suggestion

As regards the concerned technology, Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area, the sub-committee assessed that, as a result of inter-Group comparison between Study Groups and Control (Placebo) Groups of safety, the Evidence Level of the relevant literatures is B (Moderate) in evidencing relationship between adverse events and death. With no statistically significant inter-Group difference observed, only few literatures reported direct relationship between adverse events and death. Therefore, it was determined that safety of the concerned technology is not sufficiently evidenced.

As regards effectiveness of the concerned technology, such major indices as major foot amputation, minor foot amputation, amputation-free survival and improvement of ulcer healing were not reported with consistency. With no statistically significant improvement in other indices (ABI, $TcPO_2$, changes in pain, ambulatory indices, quality of life), it was determined that the concerned technology is not effective. As regards evidence level, some relevant literatures had high risk of bias when considering 'blindedness of investigators and subjects' and 'incomplete result data.' Therefore, the Evidence Level of the technology was assessed 'Moderate' or 'High.'

With the above being said, based on the assessment result by the sub-committee, the Health Technology Reassessment Committee screened Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area as follows:

The Health Technology Reassessment Committee has screened that use of Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area in inducing angiogenesis in patient with Critical Limb Ischemia for delayed foot amputation, curing of skin ulcer and improvement of function is not recommended (Recommendation Grade II). The reason for such grading is as follows:

As for safety, no statistically significant inter-Group difference in relationship between adverse events and death between Control (Placebo) Group and Study (Autologous Bone Marrow Stem Cell Treatment - in patient with Critical Limb Ischemia - Injection of Centrifuged Bone Marrow at Ischemic Area) Group was observed. Only few literatures reported direct relationship between adverse events and death. No statistically significant inter-Group difference in effectiveness-related indices was observed. Therefore, it was determined that safety of the concerned technology is not effective.

Keywords

Critical Limb Ischemia, Peripheral arterial disease, Autologous bone marrow stem cell treatment, safety, effectiveness