NECA-Health Technology Reassessment Project

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Health Technology Reassessment Report 2020

Clinical Effect of Leukocyte Transfusion and Safety of Leukocyte Stimulant

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Summary Statement

Background

The purpose of leukocyte transfusion is to supplement leukocyte (and, more specifically, granulocytes by way of transfusion in treatment and improvement of severe infection related to neutropenia. For leukocyte transfusion to take place, the leukocytes are donated by healthy donors by way of leukapheresis. These donors receive leukocyte stimulant such as G-CSF and adrenocortical hormone to improve circulating leukocyte count and collect as many granulocytes.

The technology was suggested by 'HTA Juries' in 'Survey of Research Subject 2020' conducted to fulfill social needs of medical technology re-assessment. The re-assessment protocol was determined such that the technology will be graded in the 3rd Health Technology Reassessment Committee in 2020 (Mar. 20, 2020). Taking the suggested purposes into account, this study was conducted by way of systematic literature review(SLR) in assessment of Safety of Using Leukocyte Stimulant in Blood Donor and Clinical Safety and Effectiveness of Leukocyte Transfusion in Recipients.

Organization of Sub-committee

The sub-committee was comprised of 7 different specialists (2 hemato-oncologist, 2 laboratory doctors (specialized in transfusion medicine), 1 infection physician, 1 pediatrician, 1 evidence-based medicine specialist) and held four different review meetings starting June 3 2020 and ended January 28 2021.

Methodology

Systematic literature review(SLR) was performed to assess the clinical safety and effectiveness of the technology.

Three different international literature databases and five different domestic literature databases were referred to in selection of literatures to be reviewed, under literature inclusion and exclusion criteria and by two separate reviewers.

These two separate reviewers reached a consensus in that they perform risk of bias assessment on a separate basis, using RoB and RoBANS. Data extraction was also done by these two separate reviewers, also on a separate basis, using the pre-determined data extraction format. When they failed to reach a consensus, the third reviewer came into play for discussion. The data were analyzed by way of both qualitative review and quantitative review. Evidence Level of the above-mentioned SLR was determined by way of Grading of Recommendations Assessment, Development and Evaluation(GRADE).

Result

A total of 107 different literatures (13 randomized studies, 16 non-randomized studies, 78 single-group studies) were selected.

Safety

Donor

Out of all selected literatures, 41 reported safety of leukapheresis in donors.

Among other adverse events, thrombopenia, splenic rupture and long-term side effects (oncogenesis, bone marrow disease) were retrieved out of the selected literatures. None of those literatures reported splenic rupture.

Only one out of the selected literatures reported that slight thrombopenia (PLT count 50×10^9 – 100×10^9/L) was observed in 6.5% (8/123) of the subjects.

Three out of the selected literatures reported long-term side effects. In a literature of studying effect of G-CSF and dexamethasone stimulant by comparing Leukapheresis Group and Platelet Donor Group, no statistically significant difference in occurrence of disease event was observed in 10.5 years of follow-up. In a literature studying long-term side effect, no severe long-term side effect was reported. In another literature studying the effect of blood donation, 3.9% of the subjects suffered from hypertension, diabetes or breast cancer, with less than likely possibility of blood donation affecting occurrence of disease.

Overall, it was reported that leukapheresis was tolerated quite well, with 7 literatures reporting no side effects at all. The most common leukapheresis-related side effects (including stimulant-related or precipitator-related side effects) were bone pain, myalgias and joint pain, as reported in 19 literatures (47.5%), all with temporary or slight and recovered by use of painkiller such as acetaminophen. Other side effects reported were headache, insomnia, nausea/vomiting, chilliness/fever and fatigue.

Recipient

Out of all selected literatures, 76 reported safety of leukocyte transfusion in recipients.

Among other adverse events, anaphylaxis, lung-related side effects, transfusion-related graft versus host reaction, and transfusion-derived infection were retrieved out of the selected literatures. None of those literatures reported anaphylaxis and transfusion-related graft versus host reaction.

Lung-related side effects include respiratory symptoms such as dyspnea and hypoxemia. In 3 literatures of comparative studies, the rate of such symptoms expressed in Study Groups and Control Groups were 0 - 46.2% and 0 - 54.5%. A total of 36 literatures of single-Group studies, the rate of such symptoms expressed was 0 - 52.8%. In 5 literatures reporting transfusion-related acute lung damage, 0 - 15.6% (5/32) of subjects expressed transfusion-related acute lung damage.

In 5 literatures reporting transfusion-derived infection, 0 - 5.6% of subjects expressed transfusion-derived infection.

Other adverse events reported were fever, chilliness, skin rash, frequent pulse, hypotension, nausea/vomiting.

Effectiveness

Effectiveness of leukocyte transfusion was studied in 80 literatures (23 comparative studies, 57 single-group studies) in terms of death, clinical improvement of / response on infection, fever period, days antibiotics used, and change in leukocyte count.

As for comparative studies (22 literatures), the integrated relative risk(RR) on total death rate when compared to Control Group with no transfusion received was 0.74 (95% CI 0.56-0.97, I^2=61%). In a literature studying intravascular injection of immunoglobulin(IVIG), death rate was lower in Study Group (0%, 0/21) than Control Group (35.7%, 5/14) with statistical significance (p<0.03). In 3 literatures reporting infection-related death, death rate was higher among Study Groups, with RR of 1.32 (95% CI 1.01-1.73, I^2=0%). In 10 literatures reporting clinical improvement of / response on infection, RR of leukocyte transfusion compared to Control Groups was 0.77 (95% CI 0.63-0.93, I^2=43%). No statistically significant difference in fever period and medical result related to change in leukocyte count between Study Group and Control Groups was observed.

In 57 literatures of single-group studies, death rates varied from 0% to 73.3%. The integrated event rate of death of 52 different literatures was 0.32 (95% CI 0.27-0.37, I^2=71%). According to sub-group analyses, no statistically significant difference by age, leukocyte sampling method and injection volume of leukocyte was found. In 8 literatures of infection-related death, death rates varied from 8.3% to 40%. The integrated event rate of death of 7 different literatures was 0.21 (95% CI 0.13-0.31, I^2=50%). In 44 literatures reporting clinical improvement of / response on infection, the average of 36.7 - 100% of the subjects have seen improvement / experienced response. The integrated relative risk(RR) on clinical improvement of / response on infection was 0.66 (95% CI 0.61-0.70, I^2=64%). According to sub-group analyses, no statistically significant difference by age and injection volume of leukocyte was found. Out of 32 literatures reporting change in leukocyte count, leukocyte count increased after the transfusion.

Conclusion

With limited room for generalization of the results due to widely variable target subjects, type of infection involved, methods of transfusion and leukocyte sampling and injection volume, the sub-committee suggests, based on the assessment results available, as follows:

Safety of using leukocyte stimulant in donors was confirmed based on the fact that no statistically significant inter-Group change in potential long-term side effects (cancer, etc.) was found between Study (Stimulated) Group and Control (Unstimulated) Group. The case of thrombopenia reported in a literature was very mild and deemed rather attributable to repeated leukapheresis, not use of stimulant. Overall, it was reported that leukapheresis was tolerated quite well in almost all literatures, with 7 literatures reporting no side effects at all.

Such adverse events as bone pain, myalgias, joint pain, headache, insomnia, and chilliness/fever were quite tolerable and mild such that they were cured by use of G-CSF. Therefore, it is to say that use of the stimulant in donor is safe.

As regards safety of leukapheresis in recipient, no statistically significant inter-Group difference in lung-related side effects such as dyspnea was found. As regards some literatures reporting transfusion-related acute lung damage and a number of literatures reporting respiratory symptoms such as dyspnea, it is to note that there were many subjects with underlying pneumonia derived from neutropenia. Therefore, attempt to discover relationship between these side effects and transfusion was quite limited.

As regards effectiveness of leukapheresis, the relative risk on total death rate compared to Control (Untreated) Group was low. On the contrary, response to treatment in terms of infection-related death and clinical improvement of / response on infection was quite low in Study Group. Taking into account that comparative studies have the subjects with varied characteristics (in terms of type of infection, etc.) due to the difficulties in maintaining well-controlled Control Group among severe patients considering leukapheresis, the sub-committee decided that integrated death rate

(32%), infection-related death rate (21%) and rate of improvement in infected subjects (66%) must be taken into account.

Therefore, it is to say that use of leukocyte stimulant in donor is safe. With low evidence level and widely varying results of literatures selected regarding leukapheresis, there exists a variety of factors that may impact treatment results - underlying disease, severity, infection status. Therefore, considering the fact that there are only few alternatives of ineffective antibiotics, antifungals and colony-stimulating factor, it is to say that leukapheresis is safe and effective means of treating severely infected patients in relation to neutropenia, in terms of improved survival rate and ability to control infection.

With the above being said, the Health Technology Reassessment Committee screened “Clinical Effect of Leukocyte Transfusion and Safety of Leukocyte Stimulant” as follows:

Use of leukocyte stimulant intends to improve circulating leukocyte count. Based on the fact that leukapheresis was tolerated quite well in almost all donors, no statistically significant inter-Group difference in long-term side effect was observed, and other adverse events expressed were mild, it is to say that the technology is safe.

The purpose of leukapheresis is to treat neutropenia-related severe infection and improve the patients’ condition. With the major lung-related adverse events in Study Group similar to those in Control Group and considering the fact that the subjects of single-Group studies in the selected literatures include a number of pneumonia patients, it is to say that the technology is safe. With low evidence level and widely varying results of literatures selected regarding leukapheresis, there exists a variety of factors that may impact treatment results, such as underlying disease, severity, infection status. Therefore, it is to say that leukapheresis can be considered as an alternative of ineffective antibiotics, antifungals and colony-stimulating factor.

With the above being said, the Health Technology Reassessment Committee recommended (Recommendation Grade I-b) use of leukocyte stimulant as a means of improving circulating leukocyte count, for the purpose of treating severe neutropenia-related infection and improve the patients’ condition.

Keywords

Neutropenia, Granulocyte Transfusions, Leukocyte Transfusions, Donor, Granulocyte Colony Stimulating Factor(G-CSF), Leukapheresis