ADHD 증상을 측정한 도구 중 '조사자 평가' 도구에 대해 메타분석을 실시한 결과(평균차)는 -2.31[95% CI -3.24, -1.38], '자가평가' 도구는 -3.49[95% CI -8.21, 1.23], 정신질환의 일반적 도구인 CGI도구는 -0.49[95% CI -0.67, -0.31]로 methylphenidate 복용군이 atomoxetine 복용군에 비해 ADHD 증상이 개선되는 효과가 있었다.

두 약제간의 임상시험 탈락률과 부작용 발생률 등에 대한 간접비교를 실시한 결과, 탈락률에 대한 오즈비는 1.02[95% CI 0.58, 1.81], 부작용으로 인한 탈락률은 1.13[95% CI 0.59, 2.19], 주요 부작용 중 수면장애 발생률은 0.78[95% CI 0.43, 1.40], 식욕장애 발생률은 1.20[95% CI 0.72, 1.99]으로 두 약제 사이의 탈락률 및 부작용 발생에 있어 통계적으로 유의한 차이를 보이지 않았다.

□ 결론 및 정책적 제언

본 연구를 통해 성인 ADHD 환자에 있어 methylphenidate가 atomoxetine에 비해 ADHD 증상개선에 좀 더 효과적임을 확인하였으며, 특히 OROS 제형의 methylphenidate와 atomoxetine사이에서 통계적으로 유의한 차이가 확인되었다. 그러므로 성인 ADHD 환자에서 두 약제 간의 효과를 직접비교한 적절한 연구는 부재하였으나 공통대조군을 이용한 간접비교 방법을 이용하여 두 약제간의 약물효과를 간접적으로 확인할 수 있었으며, 이는 소아 및 청소년을 대상으로 한 기존 연구(Hanwlla *등,* 2011)와 비교하였을 때에도 그 결과가 유사함을 확인할 수 있었다. 따라서 의료기술 평가에 있어 간접비교 방법이 가진 많은 제한점이 있음에도 불구하고 직접비교가 부재한 환경 하에서는 간접비교 방법을 통해 평가된 잠재적인 의료기술효과에 대해 고려해 볼 수 있을 것이다. 뿐만 아니라, 간접비교를 이용하여 산출된 치료효과는 향후 직접비교를 비롯한 다양한 연구방법을 통해 산출된 근거와의 비교를 통해 임상현장에서의 의의를 평가할 수 있을 것으로 사료된다.

〈주요어〉
간접비교, 공통대조군, 성인 ADHD, Atomoxetine, Methylphenidate

Executive Summary

Indirect Comparison Methodology research for HTA : Comparison of drug treatment effect in adult ADHD using common comparator

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☐ Introduction

In this research, we reviewed indirect comparison methodology in the context of HTA (Health Technology Assessment) when head-to-head trials are absent or lacking. As an example of HTA using indirect comparison, the study <Efficacy of Atomoxetine and Methylphenidate in Attention Deficits Hyperactivity Disorder in Adults: A Rapid Review> conducted by NECA in 2012 was selected as an exemplar. This study was a short-term rapid review and meta analysis of each treatment was not possible for given time frame.

☐ Review of Indirect Comparison Guidelines

Indirect comparison methods are used to measure the effect of treatment A compared with treatment B based on the results of trials of A and of B versus the same control (placebo or active treatment). After reviewing both domestic and international indirect comparison studies, we came to a conclusion that the method and the quality of a research need to be at the least at a parallel level and that effect modifiers used are identified. In other words, it is desirable to restrict a study design to a single design, although the paper inclusion criteria for the final indirect comparison might differ according to the key question of each research. Furthermore, an extensive comparison

of exchangeability among the included trials prior to indirect comparison is necessary. Thus, a set of pre-selected criteria for determining exchangeability is desirable for indirect comparison. However, a balance between strict examination of exchangeability and practicability of research always be reviewed, while understanding the limitation on statistical methods of indirect comparisons, i.e. it is not RCT and that it may be biased.

□ Effectiveness comparison of methylphenidate and atomoxetine in adult ADHD

For effectiveness comparison of methylphenidate and atomoxetine in adult ADHD patients, RCT (Randomized Clinical Trial) including each drugs was systematically searches and resulted in selection of 29 papers (25 researches). For the "Blinding of participants and personnel" and "Blinding of outcome assessors" criteria selected as the important key domain in this research, the risk of bias was generally considered low.

1 crossover research of 7 researches regarding atomoxetine was excluded due to the inability to retrieve result variables for met-analysis. Of 17 researches regarding methylphenidate, 7 crossover researches were excluded due to irretrievable results for meta-analysis and 1 research that used lithium as a control was also eliminated. Since each research showed different follow-up tracking period, results of 9~12 weeks for atomoxetine and 5~8 weeks for methylphenidate were integrated for meta-analysis. Results from near weeks were used for researches that did not meet the standard weeks, and mean dosages were usually 60~100 mg/day for atomoxetine and 70~80 mg/day for methylphenidate. As a result, each drug showed significant treatment effect compared to placebo through meta-analysis.

Indirect comparison methodology was implemented to compare treatment effect of the two drugs using the placebo as a common comparator. Pooled estimate using the investigator outcome CAARS-Inv:SV and AISRS as an ADHD symptom score, it showed that methylphenidate to be more significantly effective in improving ADHD symptoms compared to atomoxetine. Furthermore, when using the CGI as the general mental symptom score, methylphenidate showed significant reduction in ADHD symptoms compared to that of atomoxetine. When comparing the rate of dropout and adverse events (sleep problem/appetite problem) of the two drugs, there were no statistically significant.

☐ Conclusions

As a result of this research, the treatment effect of methylphenidate showed more significance in reducing ADHD symptoms compared to that of atomoxetine. The significant difference can be easily seen when comparing OROS methylphenidate and atomoxetine, and such effective difference has been proved through the research against children and adolescents in Hanwlla 등 (2011). Therefore, although there were not enough appropriate head-to-head trials for adult ADHD patients to compare the treatment effects of the two drugs, indirect comparison using a common comparator showed to be effective to compare each treatment effect, and have been proved by comparing its result to prior researches that were conducted against children and adolescents. Thus, also there are numerous limitations in using indirect comparison for the HTA, it can be highly considered where head-to-head trials are absent and be used for the health technology assessment. Furthermore, treatment effects resulted from indirect comparison can be later used with direct comparison and different research methods to evaluate the significance of treatment effectiveness in clinical usage.

〈Keyword〉
Indirect comparison, Common comparator, Atomoxetine, Methylphenidate,
Adult Attention Deficits Hyperactivity Disorder (ADHD),