Association of chronic spontaneous urticaria with the first exposure to general anaesthesia

To the Editor,

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by recurrent wheals and pruritus lasting more than 6 weeks; its prevalence tends to increase every year. Moreover, CSU can be a considerable social burden for patients and can substantially impair the quality of life, because of its long-term nature and unpredictable symptoms. Although various factors are associated with CSU occurrence, idiopathic cases account for approximately 80% of all CSU cases. General anaesthesia (GA) is associated with non-allergic disorders as well as various allergic disorders; previous mastocytosis or chronic urticaria is a known risk factor for severe complications of GA. However, the long-term effects of GA exposure on these allergic disorders have not been evaluated, and the relationship between GA and CSU remains unclear. Thus, we conducted a retrospective cohort study to determine whether the risk of CSU increases after exposure to GA using Korean National Health Insurance Service national sample cohort data from 2002 to 2015.

We included individuals exposed (n = 145,903) and unexposed (n = 291,806; control participants) to GA (1:2 ratio). Diagnosis of the sample cohort was based on the International Classification of Diseases, Tenth Revision (ICD-10). We divided GA exposure into intravenous injection, endotracheal tube, and mask anaesthesia, and the total duration of GA was calculated. To reduce selection bias, we set the first 2 years (2002–2003) as the washout period, and those with diagnostic codes of CSU (L501, L508, and L509) before the first recorded exposure to GA in the study period were excluded. For the GA participants, the observation began on the day of the first exposure (cohort entry date). In order to obtain a non-GA cohort, age group- (within 5 years), sex-, and income-, cohort entry date-matched controls that were unexposed to GA were randomly selected in a 1:2 ratio.

We followed up both cohorts for 2 years from the cohort entry dates to the day when the diagnostic code of urticaria was first assigned during CSU treatment, or to death, emigration, or December 2015 (the date of the last follow-up of the sample cohort), whichever came first. Participants with subsequent CSU were defined as those who had (1) more than two ICD-10 diagnostic codes of CSU, (2) more than 6 weeks of medical claims records for CSU, and (3) more than 6 weeks of a history of antihistamine prescription for treating CSU. Moreover, the CSU-related treatment record of each patient was collected even after the end of the follow-up to investigate the differences in the clinical features of CSU such as disease duration and frequency of systemic treatment in both groups.

The Kaplan–Meier method and a Cox proportional-hazard regression model were used to obtain survival curves and hazard ratios (HRs). The Cox proportional-hazards assumption of proportionality was also checked using Schoenfeld residuals. The results were considered statistically significant when the two-tailed p-value was <0.05. Statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

All characteristics, except for the Charlson-Deyo score, were not significantly different between the groups. The GA group had a higher proportion of those who had been exposed to regional anaesthesia and had a medical history of common systemic, allergic, and dermatological comorbidities compared to the non-GA group. The mean follow-up time in both groups was 1.83 years. The 2-year cumulative incidence of CSU in the GA and non-GA participants was 0.54% (270/100,000 person-years) and 0.37% (184/100,000 person-years) respectively. The Kaplan–Meier curve showed a significant difference in the cumulative incidence of CSU between the groups (log-rank p < 0.001) (Figure 1). The HRs for CSU in the cohort are summarized in Table 1. In the univariate analysis, the risk of CSU was significantly higher in the GA group than in the non-GA group (HR 1.47; 95% CI 1.34–1.62). In the multivariate analysis, after adjusting for all covariates, the statistical significance of the HR was still maintained, although the HR showed a slight decrease (adjusted HR 1.33; 95% CI 1.20–1.47). In the GA group, participants with longer exposure to GA were more likely to develop CSU, while the types of GA and the type of surgery (cancer vs non-cancer surgery) were not associated with the occurrence of CSU. The risk of CSU also differed according to the types of anaesthetic used in the GA group. The use of enflurane increased the risk of CSU (adjusted HR 1.28; 95% CI 1.05–1.58) compared to non-exposure to enflurane. However, the use of thiopental decreased the risk of CSU compared to non-exposure to thiopental (adjusted HR 0.68; 95% CI 0.52–0.90).

Subgroup analysis according to different age groups showed that only in older age groups (≥20 years old), the cumulative incidence of CSU was significantly higher in the GA cohort than that in the non-GA cohort. Likewise, multivariate Cox regression analysis stratified according to age showed that GA exposure significantly increased the risk of CSU in the older age groups.

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In analyses of clinical features of CSU, the GA group showed a higher proportion of those with >3 years of CSU than that in the non-GA group. However, the GA group showed less frequent use of systemic steroids or immunosuppressants for more than 1 month than that of the non-GA group.

Our nationwide cohort study data indicate an association between GA and CSU, but the notable relationship is not assuring. However, an evaluation of previous GA history may be needed when examining CSU patients because GA could be a risk factor for CSU.

The risk of developing CSU was 33% higher in participants with GA exposure than in those without. Moreover, the risk of CSU also increased as the duration of GA exposure increased. Based on these results, it can be assumed that various GA-related factors have the potential to induce allergic reactions. First, GA drugs can influence the immune system, with effects on pro-inflammatory cytokines including interleukin (IL)-6 and tumour necrosis factor-α (TNF-α), especially in those with longer exposure. A previous study showed that mast cells may play a pivotal role through cytokine changes of IL-6 and TNF-α in the CSU patients. Based on these results, it is unclear whether GA can directly cause CSU, but they indicate that GA can contribute to triggering CSU to some extent. This may also be associated with the increase in the HR for CSU as the GA exposure duration increases. Second, several GA drugs, especially neuromuscular blocking drugs used to induce anaesthesia, have been reported to trigger perioperative hypersensitivity reactions and CSU. Lastly, GA-related pharmacological and physiological factors, such as latex, cold conditions, or tight straps, may cross-react with various drugs and foods, triggering recurrent allergic reactions. This may explain why GA participants with CSU a longer disease duration had compared to non-GA participants with CSU and this may be related to delayed occurrence of CSU resulting in gradual increased cumulative incidence of CSU at the same rate in our study.

In our study, the occurrence of CSU was not associated with GA exposure in children. Kuo et al. showed that children with a history of GA exposure were at a lower risk of developing allergic diseases than the general population. They also suggested that GA may promote inflammatory T-helper 1 response and decrease T-helper 2 immunity, which may be protective against allergies in children.

We also showed that enflurane is an agent associated with an increased risk of CSU compared to other inhalational GA agents and thiopental reduced the risk of CSU compared to other injectable anaesthetics. Because their effects on CSU are controversial, it is difficult to conclude the existence of a direct relationship between anaesthetics and CSU risk.

To the best of our knowledge, ours is the first nationwide population-based cohort study to investigate the risk of CSU in participants with GA. However, we could not conclusively exclude study participants with a history of GA or CSU before the registration, and not consider the previous or concurrent use of all the drugs that could affect CSU development. Therefore, we set the first 2 years as the washout period and, we used a covariate-adjusted multivariate

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**Key Messages**

- The risk of CSU was significantly higher in GA group than in non-GA group.
- The occurrence of CSU was not associated with GA exposure in children.
- Longer exposure to GA was associated with a higher risk of CSU.

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**FIGURE 1** Cumulative incidence of chronic spontaneous urticaria for the general anaesthesia-exposed and unexposed cohorts
Cox model. Additionally, we performed a stratified analysis according to the status of the previous comorbidities (data not shown), and GA exposure independently increased the risk of CSU regardless of previous comorbidities.

In summary, this study suggests the possible additional role of GA in the triggering of CSU, especially in adults and longer GA exposure patients, although many unknown factors are associated with the pathophysiology of CSU. We also found that the duration of GA exposure was an important factor in the relationship between GA and CSU. Therefore, considering GA as a causative or aggravating factor may help diagnose and treat CSU.

**AUTHORS CONTRIBUTION**

Concept and design: Jin Cheol Kim, Jee Woong Choi. Acquisition, analysis, or interpretation of data: Jee Woong Choi. Drafting of the manuscript: Jin Cheol Kim, Dong Chan Kim, Young Woong Choi. Critical revision of the manuscript: Jee Woong Choi. Statistical analysis: Young Woong Choi, Jee Woong Choi. Obtained funding: Jee Woong Choi. Supervision: Eun-So Lee, Jee Woong Choi.

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**CONFLICT OF INTEREST**

None of the authors declare any conflicts of interest.

**ETHICAL APPROVAL**

This study design was reviewed and exempted from the institutional review board of Ajou University Hospital (IRB number: AJIRB-MED-EXP-21-289).

**DATA AVAILABILITY STATEMENT**

Additional information about study methods and findings are available in the following repository: 10.5281/zenodo.6534064. The raw data are not directly available because of the policy of the ethics committee of National Health Insurance Service (NHIS) in Korea. Even though the sample cohort is not an open access public
database, it is not for commercial interests but for regulating the accessibility. Therefore, only the researchers who have undergone thorough verification can use the data.

Jin Cheol Kim1
Dong Chan Kim1
Young Woong Choi2
Eun-So Lee1
Jee Woong Choi1

1Department of Dermatology, Ajou University School of Medicine, Suwon, South Korea
2Department of Anesthesiology, Korea Cancer Center Hospital, Seoul, South Korea

Correspondence
Jee Woong Choi, Department of Dermatology, Ajou University School of Medicine, Ajou University Hospital, 164, World Cup-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16499, South South Korea.
Email: dermaboy@gmail.com

ORCID
Jin Cheol Kim https://orcid.org/0000-0003-3820-8811
Dong Chan Kim https://orcid.org/0000-0003-3763-0746
Jee Woong Choi https://orcid.org/0000-0003-4631-7823

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