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No significant influence of pre-vaccination antipyretic use on specific antibody response to a BNT162b2 vaccine booster against COVID-19

Naoki Tani [a], Hideyuki Ikematsu [b], Takeyuki Goto [a], Kei Gondo [c], Yuki Yanagihara [d], Yasuo Kurata [d], Ryo Oishi [e], Junya Minami [e], Kyoko Onozawa [e], Sukehisa Nagano [f], Hiroyuki Kuwano [g], Koichi Akashi [a], Nobuyuki Shimono [h], Yong Chong [a,*]

[a] Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan
[b] Ricerca Clinica Co., Fukuoka, Japan
[c] Clinical Laboratory, Fukuoka City Hospital, Fukuoka, Japan
[d] Pharmacy, Fukuoka City Hospital, Fukuoka, Japan
[e] Department of Infectious Diseases, Fukuoka City Hospital, Fukuoka, Japan
[f] Department of Neurology, Fukuoka City Hospital, Fukuoka, Japan
[g] Fukuoka City Hospital, Fukuoka, Japan
[h] Center for the Study of Global Infection, Kyushu University Hospital, Fukuoka, Japan

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ABSTRACT

The relation between pre-vaccination antipyretic use and antibody responses to SARS-CoV-2 vaccination has been unclear. We measured the pre- and post-BNT162b2 booster spike-specific IgG titers and recorded antipyretic use and adverse reactions for SARS-CoV-2-naive hospital healthcare workers. The data of 20 cases who used antipyretics within 24 h before vaccination were compared to that of 281 controls. The post-booster geometric mean IgG titers were 15,559 AU/mL (95 % CI, 11,474–21,203) for the cases and 16,850 AU/mL (95 % CI, 15,563–18,243) for the controls (p = 0.622). No significant reduction in the frequency or severity of any of the solicited adverse reactions was found for the cases. Similar results were obtained after adjustment with propensity-score matching for demographic characteristics, baseline IgG titer, and post-vaccination antipyretic use. Antipyretic use within 24 h before vaccination would not affect mRNA COVID-19 vaccine-induced specific antibody responses and that postponement of vaccination due to pre-vaccination antipyretic use would be unnecessary.

1. Introduction

mRNA coronavirus disease 2019 (COVID-19) vaccines have shown high vaccine efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and subsequent severe or critical disease [1–4]. On the other hand, they have been known to induce more frequent adverse reactions than other existing vaccines, such as seasonal influenza or pneumococcal vaccines [2,3,5,6]. Antipyretic or pain medications (antipyretics), such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), have been used to manage adverse reactions following vaccination. Public health authorities allow the use of antipyretics to treat the reactions [7,8], but they recommend that antipyretics not be used prophylactically because of the uncertain impact on immune responses to SARS-CoV-2 vaccination [8]. Previous studies of vaccines other than COVID-19 reported that the prophylactic use of antipyretics, i.e., administration of antipyretics at the time of vaccination and subsequently every 6–8 h, interfered with antibody responses to several vaccine antigens, such as pneumococcus, Haemophilus influenzae type b, diphtheria, tetanus, hepatitis B [9–12]. There is little evidence on the relation between the prophylactic use of antipyretics and immune responses to COVID-19 vaccines.

In the real-world, some vaccinees require antipyretic medications for compelling reasons, such as a recurrent headache, incidental injury, and menstrual pain, even immediately before vaccination. The possible negative impact of the pre-vaccination use of antipyretics on immune responses to SARS-CoV-2 vaccination is of concern. To date, no studies have shown the influence of their pre-vaccination use of antipyretics on COVID-19 vaccine-induced immune responses. Herein, we investigated the influence

* Corresponding author at: Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ward, Fukuoka 812-8582, Japan.
E-mail address: jeong.yong.342@m.kyushu-u.ac.jp (Y. Chong).

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of the pre-vaccination use of antipyretics on the specific antibody titers after an mRNA COVID-19 vaccine booster. In addition, the effect of pre-vaccination use of antipyretics on the frequency and degree of adverse reactions to the booster dose was also investigated.

2. Methods

We previously investigated the association between the emergence or degree of adverse reactions and the specific antibody titers after a booster dose of BNT162b2 vaccine (Pfizer, Inc., and BioNTech) for SARS-CoV-2-naive, immunocompetent healthcare workers of Fukuoka City Hospital in Japan without immunosuppressive therapy [13]. In that analysis, the data of 20 participants who had used antipyretics within 24 h before vaccination was excluded, and the remaining 281 were analyzed. In the present study, the 20 participants who used an antipyretic before vaccination were classified into a case group and the 281 enrolled in the previous study into a control group. Serum samples were collected twice, before and approximately one month (median: 32 days, ranged 24 to 41 days) after the booster dose. The use of antipyretics before and/or after the vaccination depended on the participant. The information on self-medicated antipyretic and solicited adverse reactions was collected through a web-based self-reporting diary as previously described [13]. In brief, the use of an antipyretic within 24 h before and seven days after the booster dose were reported, including the antipyretic name, dosage, timing, and reason for use. The solicited local and systemic adverse reactions were collected daily for the seven days following vaccination. The severity of all solicited reactions was graded from 1 to 4 (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, potentially life threatening), with reference to the U.S. Food and Drug Administration guidance [14]. Local and systemic adverse event (AE) scores for each reaction, calculated by summing the maximum severity grade during the seven days, ranged from 0 to 12 and 0–32, respectively. The quantitative level of IgG antibodies for the receptor binding domain of the S1 subunit of the viral spike protein (IgG(S-RBD)) was measured using the SARS-CoV-2 IgG II assay (Abbott Laboratories Co., Ltd., Park, IL, USA). All participants provided written informed consent before undergoing any of the study procedures. The study was approved by the ethical review board of Fukuoka City Hospital (approval number 228) and registered in the University Hospital Medical Information Network-Clinical Trials Registry (registration no. UMIN000046246).

The IgG(S-RBD) titers were log-transformed for analysis. Then, the median, interquartile range (IQR), geometric mean titer (GMT), fold change, and 95 % confidence interval (CI) were calculated. Between-group differences were tested with chi-square test, Fisher's exact test, or student's *t* test. The level of significance was set at <5 %, two-sided. To minimize background bias, matching of the cases and controls was done based on propensity score matched (PSM) analysis. The matching was done with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. The propensity score model included age, sex, pre-vaccination IgG(S-RBD) titers, and the use of antipyretics after vaccination as variables. To evaluate bias reduction after PSM, absolute standardized differences were calculated again after PSM. All analyses were performed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

3. Results

The demographic characteristics of the 20 participants who used an antipyretic before vaccination are shown in Table 1. Eighteen were female, and all were under 50-years-old. Two participants had underlying diseases, one bronchial asthma and the other dyslipidemia. The most common type of antipyretic used before vaccination was an NSAID; 13 (65 %) cases, nine of whom used loxoprofen and five ibuprofen. Acetaminophen was used by eight (40 %). All participants used the antipyretic within the dosage described in the package inserts. Three participants reported using an antipyretic before vaccination for prophylaxis against adverse events, but they discontinued prophylactic antipyretic use after vaccination. Other reasons for the pre-vaccination use of an antipyretic included recurrent headache in five (40 %) cases, chronic joint or back pain in two (10 %), and dislocated finger, dental pain, and menstrual pain in one case each (5 %).

The IgG(S-RBD) titers after the booster dose of the groups with and without the pre-vaccination use of an antipyretic before PSM are compared in Table 2. No significant difference in the GMT of IgG(S-RBD) was observed (15,559 AU/mL (95 % CI, 11,474–21,203) vs 16,850 AU/mL (95 % CI, 15,563–18,243), p = 0.622). The fold change in the IgG(S-RBD) titer was also similar, 30.6-fold (95 % CI, 22.6–41.5) for the cases and 29.4-fold (95 % CI, 27.1–31.9) for the controls (p = 0.802). There was no significant difference in the frequency of any adverse reaction. No significant reduction in the degree of a reaction assessed by the AE score or maximum body temperature was found for the group with pre-vaccination use of antipyretics.

There was initially a bias in the background factors, particularly in the proportions of females and post-vaccination antipyretic use (Table s1). To correct for this, the 20 cases were matched to 20 controls using PSM to limit imbalances in the distribution of potential confounders. Standardized group differences across all covariates were less than 0.1, representing negligible differences across age, sex, pre-vaccination IgG(S-RBD) titers, and the use of antipyretics after vaccination (Fig. s1). Distributions of the propensity scores after matching were similar between the groups (Fig. s2). After PSM, there was no significant difference in the GMTs of IgG(S-RBD) of the groups (15,559 AU/mL (95 % CI, 11,474–21,203) vs 15,042 AU/mL (95 % CI, 11,003–20,564), p = 0.863), as was observed before PSM (Table 2). The fold change in the IgG(S-RBD) titer was also comparable between the groups (30.6-fold (95 % CI, 22.6–41.5) vs 29.5-fold (95 % CI, 23.8–36.6), p = 0.836). No significant differences in the frequency or severity of the adverse reactions were observed.

4. Discussion

There is concern that the use of antipyretics before vaccination possibly affects antibody responses to SARS-CoV-2 vaccination, as observed in several studies of the prophylactic use of antipyretics [9–11]. To the best of our knowledge, this is the first study to report the influence of pre-vaccination use of antipyretics on the specific antibody responses to an mRNA COVID-19 vaccine. In the present study, some participants used an antipyretic before vaccination for usual reasons that could have occurred to anyone, such as headache, chronic joint or back pain, menstrual pain, or incidental injury. No significant difference in the IgG(S-RBD) titers of the groups with and without the pre-vaccination use of antipyretics was observed. A similar result was obtained when the analysis was done after matching of the participant backgrounds by PSM. We found that antipyretic use before vaccination would not diminish the specific antibody responses induced by mRNA COVID-19 vaccines. This finding indicates that postponement of vaccination due to the pre-vaccination use of antipyretics is unnecessary, considering its negligible influence on mRNA COVID-19 vaccine-induced antibody responses.

Table 1
Demographic characteristics of the participants who used an antipyretic before vaccination.

Particitant	Age	Sex	Job category	Comorbidity	Antipyretics used before vaccination			Post-vaccination IgG(S-RBD) titer, AU/mL	Post-vaccination antipyretic use
					Type	Total dosage, mg	Reason for use		
1	22	Female	Nurse	None	Acetaminophen	400	Dental pain	828.0	Yes
2	24	Female	Nurse	None	Loxoprofen	60	Unknown	566.4	Yes
3	24	Female	Nurse	None	Ibuprofen	150	Unknown	507.6	No
4	27	Female	Nurse	None	Acetaminophen	500	Unknown	631.5	Yes
5	28	Female	Nurse	None	Acetaminophen	400	Prophylaxis against adverse events	277.6	Yes
6	34	Female	Clinical laboratory technologist	None	Acetaminophen	800	Unknown	172.0	Yes
7	35	Female	Nurse	None	Ibuprofen	150	Headache	600.8	Yes
8	35	Female	Nurse	None	Loxoprofen	60	Unknown	1430.1	Yes
9	36	Female	Nurse	None	Loxoprofen, ibuprofen	Unknown	Prophylaxis against adverse events	1015.0	Yes
10	37	Female	Nurse	None	Loxoprofen	60	Headache	250.5	Yes
11	38	Male	Occupational therapist	None	Acetaminophen	Unknown	Unknown	625.6	Yes
12	38	Female	Nurse	None	Acetaminophen	400	Prophylaxis against adverse events	280.5	Yes
13	40	Female	Nurse	None	Combination drug (acetaminophen/tramadol)	325/37.5	Back pain	464.3	Yes
14	44	Female	Nurse	None	Loxoprofen	60	Headache	1500.9	Yes
15	44	Female	Nurse	None	Loxoprofen	60	Dislocated finger	442.5	Yes
16	45	Female	Nurse	None	Loxoprofen	60	Unknown	464.9	Yes
17	45	Female	Clerk	None	Ibuprofen	200	Menstrual pain	409.0	Yes
18	45	Female	Nurse	None	Ibuprofen	Unknown	Headache	777.5	Yes
19	47	Female	Nurse	Bronchial asthma	Acetaminophen, loxoprofen	600, 60	Back pain, joint pain	468.3	Yes
20	49	Male	Doctor	Dyslipidemia	Acetaminophen, loxoprofen	300, 60	Headache	237.5	Yes

Table 2
Comparison of cases and all or propensity score matched controls.

		Pre-matching				Propensity score-matched			
		Pre-vaccination antipyretic use		Use vs non-use		Pre-vaccination antipyretic use		Use vs non-use	
		Yes (N = 20)	No (N = 281)	ratio	*p* value	Yes (N = 20)	No (N = 20)	ratio	*p* value
IgG(S-RBD) titers after vaccination	Geometric mean (95 % CI), AU/mL	15,559 (11,474–21,203)	16,850 (15,563–18,243)	0.92	0.622	15,559 (11,474–21,203)	15,042 (11,003–20,564)	1.03	0.863
	Fold change (95 % CI)	30.6 (22.6–41.5)	29.4 (27.1–31.9)	1.04	0.802	30.6 (22.6–41.5)	29.5 (23.8–36.6)	1.04	0.836
Frequency of adverse reactions									
Local reactions	Pain at injection site (%)	20 (100)	278 (98.9)	1.01	1.000	20 (100)	20 (100)	1.00	N/A
	Redness (%)	7 (35.0)	96 (34.2)	1.02	0.939	7 (35.0)	6 (30.0)	1.17	0.736
	Swelling (%)	10 (50.0)	133 (47.3)	1.06	0.822	10 (50.0)	7 (35.0)	1.43	0.337
Systemic reactions	Fever of $\geq$ 38.0 °C (%)	7 (35.0)	70 (24.9)	1.41	0.318	7 (35.0)	6 (30.0)	1.17	0.736
	Fatigue (%)	17 (85.0)	239 (85.1)	1.00	1.000	17 (85.0)	20 (100)	0.85	0.231
	Headache (%)	16 (80.0)	187 (66.6)	1.20	0.215	16 (80.0)	19 (95.0)	0.84	0.342
	Chills (%)	12 (60.0)	146 (52.0)	1.15	0.487	12 (60.0)	13 (65.0)	0.92	0.744
	Vomiting (%)	2 (10.0)	9 (3.2)	3.13	0.161	2 (10.0)	1 (5.0)	2.00	1.000
	Diarrhea (%)	3 (15.0)	35 (12.5)	1.20	0.727	3 (15.0)	4 (20.0)	0.75	1.000
	Muscle pain (%)	16 (80.0)	241 (85.8)	0.93	0.510	16 (80.0)	17 (85.0)	0.94	1.000
	Joint pain (%)	13 (65.0)	153 (54.5)	1.19	0.359	13 (65.0)	14 (70.0)	0.93	0.736
Severity of adverse reactions	Local AE score, mean (95 % CI)	2.25 (1.75–2.75)	2.00 (1.89–2.11)	1.13	0.261	2.25 (1.75–2.75)	2.15 (1.80–2.50)	1.05	0.734
	Systemic AE score, mean (95 % CI)	7.90 (6.08–9.72)	5.94 (5.49–6.38)	1.18	0.026	7.90 (6.08–9.72)	8.80 (6.73–10.87)	0.90	0.498
	Maximum BT, mean (95 % CI), ºC	37.6 (37.3–38.0)	37.4 (37.3–37.5)	1.01	0.165	37.6 (37.3–38.0)	37.5 (37.1–37.8)	1.00	0.629

CI, confidence interval; N/A, not available; AE, adverse event; BT, body temperature.

If the pre-vaccination use of antipyretics can prevent or reduce adverse reactions to COVID-19 vaccines is of great interest. To date, the effect of antipyretic medications before SARS-CoV-2 vaccination as prophylaxis against adverse reactions has not been fully investigated. In the present study, no significant differences were observed in the frequency or degree of the solicited adverse reactions related to pre-vaccination antipyretic use. Continued use of antipyretics after vaccination may help control adverse reactions, as reported in previous studies [9,12,15], however, the possible negative impact on antibody responses to COVID-19 vaccines is also of concern. Therefore, continued use of antipyretics before and after SARS-CoV-2 vaccination for prophylaxis against adverse reactions may not be recommended.

There are limitations of the present study. First, the number of participants who used antipyretics before vaccination was small, only 20, with a background bias of being predominantly female and relatively young. In addition, this study did not include those who had received immunosuppressive therapy or who had autoimmune or inflammatory disorders, but only immunocompetent participants. Although additional studies of more diverse populations are needed, our data on healthcare workers, the population with the highest risk for exposure to SARS-CoV-2 infection, would be valuable. Second, the dosage, type, and timing of pre-vaccination antipyretic medication that might affect antibody responses to vaccination were not standardized among the cases. NSAIDs have been shown to dampen inflammatory responses and antibody production in in vitro laboratory studies [16,17], while acetaminophen has been reported to possess little anti-inflammatory activity [18]. Thus, the effects of NSAIDs and acetaminophen on the antibody responses should be evaluated separately. Randomized, large scale, controlled studies are needed to overcome these limitations and to elucidate the effect of the pre-vaccination use of antipyretics on antibody responses and the prevention of adverse reactions after SARS-CoV-2 vaccination.

5. Conclusions

The pre-vaccination use of antipyretics did not interfere with the mRNA COVID-19 vaccine-induced specific IgG levels. Occasional antipyretic use within 24 h before SARS-CoV-2 vaccination would not affect specific antibody responses, thus postponement of vaccination due to the pre-vaccination use of antipyretics would be unnecessary.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100224.

References

[1] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577.
[2] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.
[3] Moreira ED, Kitchin N, Xu X, Dychter SS, Lockhart S, Gurtman A, et al. Safety and efficacy of a third dose of BNT162b2 covid-19 vaccine. N Engl J Med 2022;386(20):1910–21. https://doi.org/10.1056/NEJMoa2200674.
[4] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against covid-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385(26):2421–30. https://doi.org/10.1056/NEJMoa2115926.
[5] Reisinger K, Block S, Izu A, Groth N, Holmes S. Subunit influenza vaccines produced from cell culture or in embryonated chicken eggs: comparison of safety, reactogenicity, and immunogenicity. J Infect Dis 2009;200(6):849–57. https://doi.org/10.1086/605506.
[6] Pneumovax 23 (pneumococcal vaccine polyvalent) sterile, liquid vaccine for intramuscular or subcutaneous injection, prescribing information. http://www.merck.com/product/usa/pi_circulars/p/pneumovax_23/pneumovax_pi.pdf (Accessed on July 27, 2022).
[7] Coronavirus (COVID-19) vaccines side effects and safety. Available at: https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/safety-and-side-effects/. (Accessed on July 27, 2022).
[8] Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on July 27, 2022).
[9] Prymula R, Siegrist C-A, Chlibek R, Zemlickova H, Vackova M, Smetana J, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. The Lancet 2009;374(9698):1339–50.
[10] Doedée AMCM, Boland GJ, Pennings JLA, de Klerk A, Berbers GAM, van der Klis FRM, et al. Effects of prophylactic and therapeutic paracetamol treatment during vaccination on hepatitis B antibody levels in adults: two open-label, randomized controlled trials. PLOS ONE 2014;9:e98175-.
[11] Wysocki J, Center KJ, Brzostek J, Majda-Stanislawska E, Szymanski H, Szenborn L, et al. A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. Vaccine 2017;35(15):1926–35.
[12] Falup-Pecurariu O, Man SC, Neamtu ML, Chicin G, Baciu G, Pitic C, et al. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Hum Vaccines & Immunotherapeutics 2017;13(3):649–60. https://doi.org/10.1080/21645515.2016.1223001.
[13] Tani N, Ikematsu H, Goto T, Gondo K, Inoue T, Yanagihara Y, et al. Correlation of post-vaccination fever with specific antibody response to SARS-CoV-2 BNT162b2 booster and no significant influence of antipyretic medication. Open Forum Infect Dis 2022:ofac493. https://doi.org/10.1093/ofid/ofac493.
[14] Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Available at: https://www.fda.gov/media/73679/download. (Accessed on July 27, 2022).
[15] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancet 2020;396(10249):467–78. https://doi.org/10.1016/S0140-6736(20)31604-4.
[16] Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. Cell Immunol 2009;258:18–28.
[17] Chen JS, Alfajaro MM, Chow RD, Wei J, Filler RB, Eisenbarth SC, et al. Nonsteroidal anti-inflammatory drugs dampen the cytokine and antibody response to SARS-CoV-2 infection. J Virol 2021;95(7). https://doi.org/10.1128/JVI.00014-21.
[18] Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. Front Pharmacol 2020;11:. https://doi.org/10.3389/fphar.2020.580289580289.