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Effect of regular administration of antipyretic analgesics on fever following COVID-19 mRNA vaccination.

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Abstract

This retrospective study evaluated the impact of the regular use of antipyretic analgesics on fever and other adverse reactions following administration of the COVID-19 mRNA vaccine（BNT162b2）in inpatients at a convalescent rehabilitation ward. A total of 83 patients who received two doses of the BNT162b2 mRNA vaccine between May and December 2021 were included. Patients were divided into two groups: those who regularly used antipyretic analgesics for disease treatment（medication group, n = 24）and those who did not（non-medication group, n = 59）. We assessed the frequency of adverse reactions, the occurrence of fever, and changes in body temperature over five days post-vaccination. The results showed no significant differences in the frequency of fever or adverse reactions between the two groups for both the first and second doses. Repeated measures ANOVA revealed significant main effects of time on body temperature, but no significant main effects of group or interaction effects. These findings suggest that regular prophylactic use of antipyretic analgesics does not effectively suppress fever or other adverse reactions after mRNA vaccination. Careful consideration is needed when determining the appropriateness of prophylactic antipyretic use based on individual cases.

Key words: COVID-19, mRNA vaccine, adverse reactions, prophylactic use, antipyretics

Introduction

Coronavirus disease 2019（COVID-19）caused a global public health crisis beginning in 2020, prompting the rapid development of effective vaccines. Among these, messenger RNA（mRNA）vaccines（BNT162b2 and mRNA-1273）have demonstrated high efficacy and safety against SARS-CoV-2 and are important prophylactics for preventing severe disease and curbing transmission.[1,2)] Since the special emergency approval of mRNA vaccines in Japan in February 2021, a government-funded vaccination program has been implemented. As of April 2024, the primary vaccination rate has exceeded 80%, and the third-dose coverage has reached 67.1%, making a substantial contribution to the achievement of herd immunity.[3)]

The high efficacy of mRNA vaccines has been confirmed in international clinical trials; however, it has also been reported that a wide range of adverse events frequently occur following vaccination. These adverse events include local reactions, such as pain and swelling, and systemic symptoms such as fever, fatigue, headache, and arthralgia.[4)] Among these, fever is a particularly important adverse event in the context of rehabilitation and care, as it can interfere with patients' activities of daily living and work performance, potentially leading to a decline in quality of life.

Antipyretic analgesics, such as acetaminophen（APAP）and non-steroidal anti-inflammatory drugs, are widely used as symptomatic treatments to alleviate adverse events following vaccination. However, there is currently no consensus regarding the effectiveness of pre-vaccination use of these medications in reducing adverse events, particularly

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when administered regularly as a prophylactic measure. A previous study reported that pre-vaccination use of antipyretic analgesics suppresses immune responses by lowering antibody titers.[5] On the other hand, another study reported that the use of antipyretics after vaccination does not significantly impact immune responses.[6] It has been suggested that the effect varies depending on the vaccine type, drug class, and timing of administration. This uncertainty surrounding the impact on immunogenicity remains one of the key factors complicating the recommendation of prophylactic antipyretic use.

Due to concerns about systemic adverse reactions, particularly fever, and their potential impact on daily activities, such as work, some vaccine recipients opt for prophylactic use of antipyretic analgesics. However, the scientific evidence supporting their efficacy in reducing adverse reactions remains limited.

This study aimed to assess the real-world clinical impact of scheduled antipyretic analgesic use, administered for unrelated medical conditions, on the incidence of fever and other adverse reactions following COVID-19 mRNA vaccination. We conducted a retrospective analysis in patients who received the vaccine during hospitalization in a convalescent rehabilitation ward.

Methods

1. Subjects

This study included consecutive inpatients who were hospitalized at Sanyudo Rehabilitation Center and completed two doses of the BNT162b2 mRNA COVID-19 vaccine during the same hospitalization between May and December 2021. Exclusion criteria were: incomplete vaccination data, use of immunosuppressive agents that could affect vaccine response, and differences in the type or dosage of antipyretic analgesics between the two doses. Adherence to scheduled antipyretic analgesics was verified using medication administration records.

2. Classification and outcomes

Patients were divided into two groups: a 'medication group' that received scheduled antipyretic analgesics for pain unrelated to vaccine side effects, and a 'non-medication group,' that did not receive such medications. Between-group comparisons were made for the presence of fever, other adverse reactions, and temporal changes in body temperature from day 0 to day 5 post-vaccination. Adverse reactions were identified from medical records. The highest value among at least two daily temperature measurements was used for analysis. Fever was defined as a body temperature of ≥ 37.5°C, consistent with the threshold commonly applied in clinical practice and public health surveillance in Japan.[7] [8]

3. Statistical analysis

Fisher's exact test was used to compare the incidence of adverse reactions and fever between groups. Repeated measures ANOVA was employed to assess temporal variations in body temperature. To evaluate the potential impact of age differences between groups on the outcomes, a stratified analysis was conducted according to age category (<75 years vs. ≥75 years). Statistical analyses were performed using EZR (version 1.61), with a two-sided significance level set at $p < 0.05$.

4. Ethical considerations

The study protocol was approved by the Ethics Committee of the Sanyudo Hospital Foundation.

Results

Of the 109 patients who received two doses of the COVID-19 mRNA vaccine during the study period, 83 were included in the analysis (medication group = 24, non-medication group = 59). The medication group was significantly older; however, no significant difference in sex distribution was found between the groups (Table 1). The antipyretic analgesics used in the medication group included acetaminophen (n = 14), loxoprofen sodium (n = 5), celecoxib (n = 4), and a combination of acetaminophen and celecoxib (n = 1).

The incidence of adverse reactions is summarized in Table 2. Following the first dose, adverse reactions occurred in 13 patients (54.2%) in the medication group and 28 patients (47.5%) in the non-medication group, and fever occurred in two patients (8.3%) and four patients (6.8%),

Table 1. Patient Characteristics

	Medication Group	Non-Medication Group	p-value
Number of cases	24	59	
Age（years）	84（33-91）	72（41-91）	0.008 a)
Sex（Male / Female）	8 / 16	33 / 26	0.089 b)
Types of Analgesics Used			
Acetaminophen	14（58%）	0	
Loxoprofen Na	5（21%）	0	
Celecoxib	4（16%）	0	
Acetaminophen + Celecoxib	1（4%）	0	
Primary Diagnosis			
Cerebrovascular disease	5（21%）	48（81%）	< 0.001 b)
Musculoskeletal disease	15（63%）	8（14%）	0.003 b)
Other	4（16%）	3（5%）	0.942 b)

Age is expressed as median（range）. Types of analgesics and primary diagnoses are shown as number of cases（percentage）. a）Mann-Whitney U test; b）Fisher's exact test

Table 2. Incidence of Adverse Reactions

	Medication Group（N = 24）		Non-Medication Group（N = 59）		p-value
	1st dose	2nd dose	1st dose	2nd dose	1st dose / 2nd dose
Adverse reactions（%）	13（54.2%）	20（83.3%）	28（47.5%）	48（81.4%）	0.634 / 1.000
Systemic					
Fever	2（8.3%）	1（4.2%）	4（6.8%）	6（10.2%）	1.000 / 0.667
Fatigue	0	3（12.5%）	2（3.4%）	7（11.9%）	1.000 / 1.000
Headache	0	0	0	3（5.1%）	1.000 / 0.550
Nausea	0	1（4.2%）	0	0	1.000 / 0.294
Facial flushing	0	0	0	1（1.7%）	1.000 / 1.000
Arthralgia	0	0	0	1（1.7%）	1.000 / 1.000
Local					
Pain	8（33.3%）	10（41.7%）	17（28.8%）	17（28.8%）	1.000 / 0.289
Local heat	2（8.3%）	1（4.2%）	3（5.1%）	9（15.3%）	0.645 / 0.260
Swelling	1（4.2%）	3（12.5%）	1（1.7%）	2（3.4%）	0.539 / 0.147
Itching	0	1（4.2%）	1（1.7%）	1（1.7%）	1.000 / 0.505
Redness	0	0	0	1（1.7%）	1.000 / 1.000

respectively. After the second dose, adverse reactions were reported in 20 patients（83.3%）in the medication group and 48 patients（81.4%）in the non-medication group, and fever was observed in one patient（4.2%）and six patients（10.2%）, respectively. There were no significant differences between the groups in the incidence of adverse reactions or fever after either dose. Because the medication group was significantly older, a stratified analysis by age category（<75 years vs. ≥ 75 years）was conducted to evaluate the potential impact of age on outcomes. This analysis showed no significant differences in the incidence of fever between the groups（Table 3）.

Figures 1 and 2 show temporal changes in body temperature over the 5 days following vaccination

Table3.　Incidence of Fever by Age Category（< 75 years vs. ≥ 75 years）

Age category	Medication Group (N=24)	Non-medication Group (N=59)	p-value
< 75 years			
1st dose	1 / 8（12.5%）	1 / 32（3.1%）	0.364
2nd dose	1 / 8（12.5%）	2 / 32（3.1%）	0.498
≥ 75 years			
1st dose	1 / 16（6.3%）	3 / 27（11.1%）	1.000
2nd dose	0 / 16（0.0%）	4 / 27（14.8%）	0.279

Data are shown as number of cases with fever / total number of cases in each age category（%）. Fisher's exact test was used for comparisons between groups.

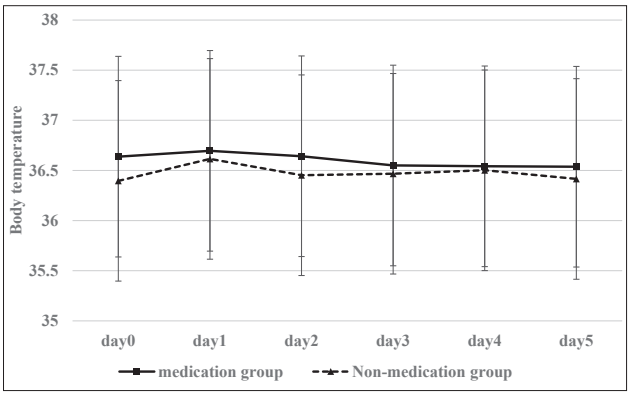

Figure 1.　Temporal changes in body temperature during the 5 days after the first vaccine dose

A significant main effect of time was observed（p = 0.033）. However, post hoc pairwise comparisons with the Bonferroni correction did not reveal any significant differences between individual time points.

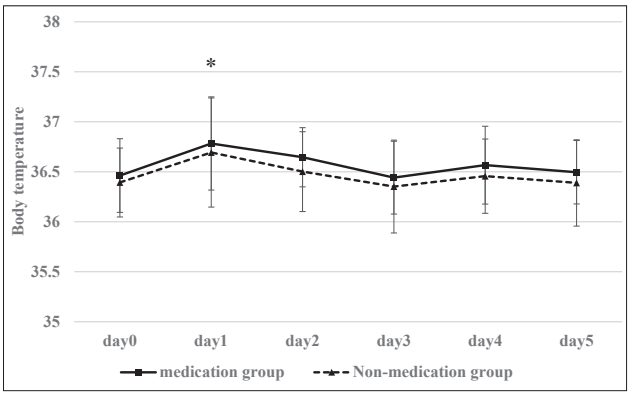

Figure 2.　Temporal changes in body temperature during the 5 days after the second vaccine dose

* A significant main effect of time was observed（p < 0.0001）. Post hoc pairwise comparisons with the Bonferroni correction revealed the following significant differences: day 0 vs. day 1（p = 0.0007）, day 1 vs. day 3（p = 0.0001）, day 1 vs. day 4（p = 0.0095）, and day 1 vs. day 5（p = 0.0001）.

for the first dose and second dose, respectively. Repeated measures ANOVA revealed that, for both doses, body temperature rose on Day 1 and declined on Day 2 in both groups. For the first dose, there was a significant main effect of time（F（5, 400）= 2.45, p = 0.033）. However, the main effect of group（F（1, 80）= 2.66, p = 0.107）and the interaction between group and time（F(5, 400）= 0.95, p = 0.449）were not significant. For the second dose, there was a significant main effect of time（F（5, 375）= 11.49, $p = 2.48 \times 10^{-10}$）; however, neither the main effect of group（F（1, 75）= 1.35, p = 0.250）nor the group-by-time interaction（F（5, 375）= 0.37, p = 0.870）reached statistical significance.

Discussion

This retrospective study evaluated the impact of scheduled antipyretic analgesic use, administered for underlying medical conditions, on the incidence of fever and other adverse reactions following COVID-19 mRNA vaccination in patients hospitalized in a convalescent rehabilitation ward. The findings showed no clear evidence that scheduled use of antipyretic analgesics reduced the frequency of fever or overall adverse reactions after either the first or second vaccine dose. Additionally, no significant differences were observed in the temporal changes in body temperature over the 5-day post-vaccination period between patients who received antipyretics and those who did not.

In the longitudinal analysis of body temperature after the second dose of the COVID-19 mRNA vaccine, a significant main effect of time was observed, with temperatures peaking on Day 1 and subsequently declining. This pattern aligns with the well-recognized trajectory of vaccine-induced reactogenicity. The significant main effect of time likely reflects this canonical response profile,

whereas the absence of a significant main effect of group or a time-by-group interaction suggests that scheduled therapeutic antipyretics did not alter this temporal pattern. These findings imply that the prophylactic use of antipyretic analgesics did not influence the natural course of post-vaccination fever.

Despite the lack of pre–second-dose temperature data, our finding of a significant main effect of time after dose two aligns with the well-described reactogenicity profile of mRNA COVID-19 vaccines, wherein systemic reactions, including fever, occur more frequently after the second dose than after the first. This pattern has been consistently observed in the pivotal BNT162b2 trial and cohorts in Japan.[1) 9)]

Our findings do not strongly support the routine prophylactic use of antipyretic analgesics as an effective strategy for preventing vaccine-related adverse reactions, and support the practical approach of managing such reactions symptomatically as they arise.

The present findings are generally consistent with those of a large-scale adverse event survey conducted in Japan.[3)] While many studies have reported a high incidence of systemic adverse reactions, such as fever and fatigue, following mRNA vaccination, there is limited evidence that the incidence of these reactions is significantly influenced by specific factors.[4)] The lack of a reduction in fever or adverse reaction frequency among patients receiving scheduled antipyretic analgesics suggests that prophylactic administration was not effective.

Previous studies have shown conflicting findings regarding the association between antipyretic analgesics and vaccine immunogenicity. A study reported that APAP use after pediatric vaccination reduced antibody titers;[5)] however, another study reported that symptomatic use of APAP did not significantly affect immune responses to mRNA vaccines.[10)] A proposed mechanism for reduced immunogenicity involves interference with early innate immune responses and subsequent antigen presentation and T-cell activation;[11)] however, detailed investigations in humans receiving mRNA vaccines are lacking. As this study did not assess immune responses, the impact of antipyretic use on immunogenicity remains to be elucidated. Nonetheless, the absence of a fever-suppressing effect suggests limited benefit from prophylactic administration. This aligns with current WHO and CDC guidance, which discourages pre-vaccination use of antipyretics but permits their post-vaccination use for symptomatic relief.

Several factors may explain why a prophylactic effect of antipyretic analgesics was not observed in this study. First, the medications were administered on a scheduled basis for pain management, not for fever prevention, which may have involved different mechanisms or timing compared to prophylactic use. In addition, variability in the types and doses of antipyretics used, as well as differences in patients' underlying conditions and metabolic status, may have contributed to inconsistent effects on adverse reactions. It has also been suggested that specific antipyretic agents selectively influence particular vaccine-induced inflammatory pathways,[11)] thus, the inclusion of multiple agents in this study may have masked any potential effects.

This study has several limitations. A key limitation is that daily body temperature data in the days preceding the second dose (e.g., days −5 to 0) were not collected; therefore, we could not directly assess whether short-term pre-vaccination fluctuations were associated with post-vaccination fever. Future studies should incorporate pre-dose baseline temperature trajectories to clarify this potential relationship. First, its retrospective design made it difficult to control for confounding factors such as underlying diseases and potential drug interactions. Additionally, the heterogeneity in the types, dosages, and indications of antipyretic analgesics may have limited the ability to uniformly assess their effects on adverse reactions. Furthermore, the small number of participants who received antipyretic/analgesic agents precluded a meaningful subgroup analysis by drug type. Specifically, among the 24 participants in the medication group, 14 received acetaminophen, 5 received loxoprofen, and 5 received celecoxib. Given this limited sample size, particularly for low-frequency events such as fever, the statistical power to detect potential differences between these subgroups would be extremely low. This limitation should be addressed in future

studies with larger sample sizes. The relatively small sample size may have limited the statistical power to detect adverse reactions with low incidence rates, such as fever, thereby reducing the ability to identify significant differences between groups. Therefore, these findings do not definitively rule out the potential efficacy of prophylactic antipyretic use. Further large-scale prospective interventional studies with standardized medication types, dosages, and indications are warranted.

Conclusion

The findings of this study suggest that scheduled antipyretic analgesic use for therapeutic purposes does not have a clear preventive effect on fever and other adverse reactions following COVID-19 mRNA vaccination. Therefore, our findings do not support routine prophylactic administration of such medications, and instead support symptomatic treatment after vaccination. However, given patients' concerns about adverse reactions and the potential impact on daily life, it is important to carefully assess the appropriateness of symptomatic antipyretic use on a case-by-case basis, taking into account individual clinical and psychological contexts. To establish evidence-based recommendations, future studies should conduct prospective interventional investigations using standardized agents and administration schedules to evaluate the effectiveness of prophylactic use.

Conflicts of Interest

There are no conflicts of interest to declare.

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