The Effect of Antipyretics on Antibody Production in Pediatric Patients Post-Vaccination

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ABSTRACT

The COVID-19 pandemic and subsequent vaccine administration renewed the question of the potential effect that antipyretics have on antibody levels post-vaccination in pediatric patients. Many patients take antipyretics to reduce side effects and fevers as they have anti-inflammatory properties. We reviewed the literature for studies examining the question of whether the consumption of antipyretics reduced post-vaccination antibody titers. We found that there is a correlation between antipyretics decreasing antibody production in the pediatric population when given prophylactically. However, to confirm these results more in depth studies are required. Our PICO question allowed us to narrow our focus into the pediatric population, antipyretic intervention, and antibody levels. Our results reflect a significant decrease in antibody levels, but antipyretics do not affect clinical efficiency of the vaccines. Our world relies on vaccine technology and it has allowed us to survive pandemics like the COVID 19 outbreak. In order to keep using these innovations safely, more trials must be conducted.

Background

The advent of SARS-CoV-2 vaccines were a welcomed innovation amongst the havoc and uncertainty of the global COVID-19 pandemic. However, many effects and questions pertaining to immunization efficacy and adverse effects have not been answered. Though there are numerous types of vaccines, they are identical in objective: stimulating antibody production (Pulendran, B., & Ahmed, R. 2011.) In the setting of the new mRNA vaccines the common question of whether antipyretic usage post-vaccination affects immunologic response has been renewed. Many vaccines cause adverse reactions in patients which can be painful and discomforting. Whether it be for injection site soreness, fever, or prophylaxis, antipyretics are the most common medication taken for vaccine adverse effects (de Martino et al., 2017.) Despite their frequent use, however, the impact of these agents on immunogenicity as measured by neutralizing antibodies, remains unclear (Park, J.Y. et Al, 2021.)

For children, or immunodeficient patients especially, the intake of antipyretics may be of even more significance given their generally increased susceptibility to vaccine preventable infections. Infants and newborns have immature immune systems and are more susceptible to invading pathogens, thus the effectiveness of vaccines to prevent infection are vital (Simon, A. K et al. 2015, Kloc M et al 2020.) Animal studies as well as in vitro studies in human samples have demonstrated a significant decrease in antibody production in the setting of antipyretic medications (Culbreth et al 2015, Bancos et al. 2009, Lafleur et al. 2022, Chen J et al. 2021.) Over 80.4% of all children receive a vaccination before the age of two years old, therefore, the question of damaged immunity is prevalent and populated (CDC 2022.) Antipyretic medications have been used for decades to manage adverse reactions by vaccination in pediatric and adult populations. It is important that these medications are safe for vaccine efficacy in every patient. In this study we review published literature that explores this question of whether antipyretic medications following vaccination impacts antibody levels.

Methods and Materials

We reviewed medical literature using electronic bibliographic databases, PubMed and Google Scholar in November, 2022. Our review of the literature was not limited by year and included only English language reports. This search did not exclude preprints from Medrxiv. Eleven papers were found that answered our question. We used keywords: analgesics, antipyretics, vaccination, and antibodies. Standardized screening procedures were used with 2 reviewers. We defined antipyretics to include acetaminophen, paracetamol and the NSAIDs most commonly utilized to prevent and relieve vaccine side effects (Skelly et Al. 2002.)

Our main criteria for study inclusion reported consumption of an antipyretic medication prior to and following vaccination, and measurement of vaccine induced antibody levels in the setting of any type of vaccination. Additionally, for background we reviewed studies exploring the mechanisms of antipyretics effect on post-vaccination immune responses. In our review, systematic reviews were weighted more heavily than single-centered studies and those with greater participant numbers were also considered heavily.

Results

We found eleven studies which explored the impact of the use of antipyretics on antibody levels post-vaccination (Table 1.) Of the most heavily weighted studies, the common outcome was a significant decrease in immunoglobulin levels but not a clinically significant decrease (Table 1.) Often the antibody levels decreased but no study reported levels below the predetermined seroprotective threshold. There was a correlation in the timing of antipyretic injection, for patients medicated prophylactically: a greater decrease in antibody levels was found (Table 1.) The prophylaxis combined with developing infants and children below the age of 4 years old also had a decreased tendency in antibody GMC (Table 1.) Type of antipyretic: acetaminophen, ibuprofen, and other NSAIDs tested had no effect on the antibodies. Similarly, no certain demographic other than age was affected. Many of the systematic reviews used SARS-CoV-2 vaccines while others tested Diphtheria toxoid, tetanus and other pneumococcal vaccines. From the data provided, there is a correlation between pneumococcal vaccines with antipyretics being more likely to decrease antibodies because of their structure (Table 1.)

Discussion

This information has tremendous clinical impact and needs to be assessed in larger, randomized, controlled trials for more accurate data. The human body as a system is more complex than singular cells, therefore, the results from paper 4 are not representative of the realities of antipyretics on antibody levels in the body. Similarly, the studies done on animals can never fully mimic the outcomes in a human body. Other than a few outliers, all patients regardless of NSAID usage and immune development, formed adequate antibodies that were protective against pathogens and infection and above the seroprotective threshold. Antipyretics have immunosuppressant properties that inhibit the production of antibodies. Many of these medications have Cyclooxygenase-2 (Cox-2) inhibitors. Cox-2 is an enzyme that speeds up the formation of substances that cause inflammation and pain. Also known as prostaglandin-endoperoxide synthase 2, Cox-2's absence doesn't allow B lymphocytes to fully germinate and produce sufficient antibodies as it is not inflamed (National Cancer Institute n.d.) The type of anti-inflammatory was not significant to the data and neither was the dosage, but the age and timing were because, if the Cox-2 is not inhibited previous to injection, it has the time to produce some antibodies before neutralization. Similarly, with pediatric patients that are developing immune systems, their bodies are trying to survive general pathogens, so adding a vaccine and an antibody dampener, leaves them vulnerable and with significantly lower antibodies.

Table 1: Antipyretic effect on antibody levels

Table 1

Author name/Journal/Date published	Type of study	n=	Vaccines	Age Range	Antibody outcome
Tani et al. Elsevier February 2022	Cohort Study	343	COVID-19	29-50	No impact, except for with prophylactic administration
Lafleur et al. MedRxiv October 2022	Survey	6010	COVID-19	18-50	No detriment seen in patients who took analgesics post vaccination
Das et al. PLOS one September 2014	Systematic review	5077	DTwP primary and booster, DTaP, PHiD-CV, HiB, HepB, IPV	Less than or equal to 6 years old	Antibody levels significantly Less in prophylactic antipyretic group, but not below seroprotective levels
Chau-Glendinning et al. Journal of Family Medicine April 2020	Systematic review	1050	DTaP/HBV/ IPV/HiB/ PVC13	Less than or equal to 6 years old	Antibody levels significantly less in prophylactic antipyretic group but not below seroprotective levels using acetaminophen and ibuprofen
Kobashi et al. PLOS one June 2022	Observational study	231	COVID-19	18-78	Daily administration of antipyretic analgesics was significantly associated with a lower antibody titer, Similarly, one administrated prophylactically, the antibody levels or decreased.
Brown et al. Family Physician Inquires Network February 2020	Meta-analysis	7021	Diphtheria,Tetanus, Haemophilus influenza, Hep B, Pertussis	6 weeks old - 6 years old	Claimed that prophylactic antibiotic administration did reduce immunological responses, but not more than the seroprotective threshold.
Ooi et al. Nature Partner Journal March 2022	Review article	5335	COVID-19	6 weeks old - greater than 65 years old	This review stated that more studies are needed to make a definite conclusion.
Saleh et al. Taylor & Francis 2016	Review article	7872	Diphtheria,Tetanus, Haemophilus influenza, Hep B, Pertussis	Infants - greater than 65 years old	Found that antipyretics affected immunity at the time of vaccination, not as treatment thereafter. Reported that more trials and data are needed to clearly evaluate the effect on immunogenicity
Koufoglou et al. Biomedical Central March 2022	Systematic review	2775	Pneumococcal, conjugate vaccines	2 years old and up	Stated a decrease in antibody's for some PCV antigens, but overall more tests are needed to make a proper conclusion.
Arijit Sil et al. Elsevier March 2017	Secondary analysis of a vaccine study	975	DTwP-HepB-Hib combination vaccine	Infants 6-8 weeks old	Antibody levels significantly Less in prophylactic antipyretic group, but not below seroprotective levels
Park et al. Journal of Clinical Medicine June 2021	Cross-sectional study	182	COVID-19	37 - 51 years old	No evidence supported blunted antibody response with the use of acetaminophen.

Limitations

There were many limitations on this paper: this was not a systematic review of the literature. lack of randomized control trials and limited pediatric studies. We are unable to separate effects from various antipyretic agents and classes, nor were we able to distinguish impact on various vaccination types.

Conclusions

Antipyretics negatively impact the level of neutralizing antibodies following vaccination. The clinical significance of this is unclear. More higher quality studies are required to explore this question more completely. However, for the clinical impact of this data, there is a severe lack in RCT's. In order to attain maximum efficiency and protection for all vaccinated children, the effects of antipyretics need to be explored deeper.

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