Original Article

Effect of Perioperative Acetaminophen on Body Temperature after Cardiovascular Surgery with Cardiopulmonary Bypass: A Single-Center Retrospective Study

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ABSTRACT

Context: Postoperative hyperthermia, which may lead to cognitive decline, is a common complication of cardiovascular surgery with cardiopulmonary bypass (CPB).

Aims: The aim of this study was to examine the effectiveness of perioperative intravenous acetaminophen on body temperature in adult patients after cardiovascular surgery with CPB.

Settings and Design: This was a single-center retrospective study focusing on adult patients who underwent elective cardiovascular surgery with CPB at a university hospital in Japan.

Subjects and Methods: Patients were divided into two groups based on whether they received acetaminophen perioperatively. In the acetaminophen group, 15 mg/kg intravenous acetaminophen solution was infused at 30 min after discontinuation of CPB and every 6 h after intensive care unit (ICU) admission.

Statistical Analysis Used: The primary outcome was the maximum axillary temperature within 12 h after ICU admission. The effects of acetaminophen on postoperative body temperature were estimated by the standardization and inverse probability weighting using propensity scores.

Results: A total of 201 patients were included in the final analysis (acetaminophen group, n = 101; non-acetaminophen group, n = 100). The maximum axillary temperature within 12 h after ICU admission was 37.20 ± 0.54 C in the acetaminophen group and 37.78 ± 0.59 C in the non-acetaminophen group. Acetaminophen lowered the standardized mean of primary endpoint (0.54 C, 95% confidence interval, 0.69 to 0.38) compared to non-acetaminophen.

Conclusions: Perioperative intravenous acetaminophen inhibited body temperature elevation after cardiovascular surgery with CPB, compared with the non-acetaminophen group.

Keywords: Acetaminophen, body temperature, cardiopulmonary bypass, cardiovascular surgery, postoperative hyperthermia

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INTRODUCTION

In humans, core body temperature is tightly controlled within a narrow range of 0.2–0.5°C (inter-threshold range) at around 37.0°C by the thermoregulatory system.[1] Inflammation caused by surgical stress can shift the inter-threshold range toward higher core body temperature. Cardiopulmonary bypass (CPB) is known to strongly induce inflammatory response.[2] Therefore, inter-threshold range can shift to higher core body temperature immediately after cardiovascular surgery with CPB, and at least 38% of patients had clinically hyperthermia (>38.5°C) after surgery.[3] Under this condition, autonomic thermoregulatory responses, such as peripheral vasoconstriction and shivering, occur even if the core body temperature is around 37.0°C.[4] It is well-known that postoperative shivering exacerbates the demand-and-supply balance of oxygen in the myocardium, leading to myocardial ischemia and arrhythmia.[5] Therefore, autonomic thermoregulatory responses must be avoided in patients who undergo cardiovascular surgery.

In theory, raising the core body temperature over the threshold can prevent shivering. However, hyperthermia after cardiovascular surgery with CPB is associated with deterioration in cognitive performance.[6,7] Grocott and colleagues demonstrated that postoperative hyperthermia is associated with cognitive dysfunction at 6 weeks following coronary artery bypass graft surgery.[7] Therefore, post-CPB hyperthermia should be avoided. Nevertheless, there are no clinical recommendations to prevent hyperthermia or shivering after cardiovascular surgery.[8]

Acetaminophen, an old antipyretic analgesic, has been used safely. It can maintain inter-threshold range within the normal range by regulating the hypothalamic heat-regulating center.[9] Thus, the scheduled administration of acetaminophen may maintain normothermia without shivering during the perioperative period. Recently, a randomized clinical trial showed that among older patients undergoing cardiac surgery, postoperative use of scheduled intravenous acetaminophen, combined with intravenous propofol or dexmedetomidine, significantly reduced the incidence of postoperative delirium compared with placebo.[10] However, there are no reports on the antipyretic effects of acetaminophen on hyperthermia after adult cardiovascular surgery with CPB.

We, therefore, hypothesized that perioperative intravenous acetaminophen inhibits the elevation of body temperature after cardiovascular surgery with CPB. The aim of this study was to examine the effectiveness of acetaminophen on body temperature management in adult patients after cardiovascular surgery with CPB.

SUBJECTS AND METHODS

This single-center, retrospective cohort study was approved by our Institutional Ethical Committee (approval No. 17112019), which follows the Declaration of Helsinki. Owing to anonymity, the requirement for informed consent was waived. This manuscript adheres to the STROBE guidelines [Supplemental Digital Content 1].

Patients

Adult patients aged >18 years with American Society of Anesthesiologists (ASA) physical status classification I to III, undergoing elective cardiovascular surgery with CPB from January 2014 to January 2016 were divided into two groups, the acetaminophen group (Group A) and the non-acetaminophen group (Group N), based on whether they received acetaminophen perioperatively. However, the perioperative administration of intravenous acetaminophen was started in October 2014 in our hospital, and whether intravenous acetaminophen had to be administered was decided depending on each anesthesiologist and intensivist. Additionally, the protocol of scheduled intravenous acetaminophen was not standardized. Therefore, no patient received acetaminophen before September 2014, and there were many patients who did not receive intravenous acetaminophen according to the following protocol even after the perioperative administration of intravenous acetaminophen was started. Because of this, patients who did not receive intravenous acetaminophen according to the protocol were excluded from this study. Other exclusion criteria were history of hemodialysis and liver disease, infectious endocarditis and aneurysm, a case with ventricular assisted device, intra-aortic balloon pumping, or percutaneous cardiopulmonary support.

The following protocol was used for the perioperative administration of acetaminophen in our hospital: 15 mg/kg intravenous acetaminophen was infused at 30 min after discontinuation of CPB and every 6 h after intensive care unit (ICU) admission. Postoperative administration of scheduled intravenous acetaminophen was performed until the patient was discharged from the ICU. If the patient's weight was over 60 kg, 1000 mg intravenous acetaminophen was infused, and the total daily dose was up to 4000 mg.

All patients were equipped with radial arterial catheter, central venous catheter, bispectral index (BIS), and

transesophageal echocardiography for routine anesthetic monitoring. However, all patients were not equipped with a pulmonary artery catheter. Patients received total intravenous anesthesia during surgery: continuous infusions of remifentanil 0.5 μg/kg/min and propofol 2–8 mg/kg/h according to BIS of 40–60 for anesthesia. Rocuronium was used for muscle relaxation. Intraoperatively, esophageal and rectal temperatures were continuously measured for all patients. Before CPB, no warming device, including a forced warming device, was used. The rectal temperature was controlled within 32.0 to 34.0°C during aortic-cross clamping. When weaning off CPB, rectal temperature was within 36.0–37.0°C in our procedure. After CPB, intravenous fluid warming device (LEVEL1® HL-90, Smiths Medical, MA) was used for maintaining the body temperature. Before the end of surgery, fentanyl was administered for postoperative analgesia and inhibition of autonomic thermoregulatory responses, and the doses were decided by each anesthesiologists. From the end of surgery until discharge from the ICU, axillary temperature of all patients was recorded at an arbitrary time, which was decided by the nursing staff. Other site of body temperature was not measured in any patient. After ICU admission, the patients were warmed by forced air-warming devices until 36.5°C of axillary temperature or peripheral vasodilatation. After surgery, all patients were transferred to ICU under sedation and tracheal intubation. The sedative agents administered after ICU admission were propofol-based, with or without dexmedetomidine and fentanyl, depending on each intensivist. The timing of weaning from mechanical ventilation was also determined by each intensivist.

We administered cefazolin, a first-generation cephalosporin, for the prevention of surgical site infections. After induction of anesthesia, 1 g cefazolin was infused every 3 h until the end of surgery. After surgery, the dose of cefazolin was determined according to the creatinine clearance, and the administration was continued until 48 h.

Study endpoints

The primary outcome variable was the maximum axillary temperature within 12 h after ICU admission. The secondary outcome variable was the incidence of hyperthermia within 12 h after ICU admission. Previous studies have shown that the axillary temperature of healthy adults range from 36.2°C to 37.5°C.[11] Therefore, the postoperative hyperthermia was defined based on axillary temperature >37.5°C.

Additionally, postoperative clinical course was also considered as the study endpoint: ventilation time in ICU, leukocyte, and C-reactive protein (CRP) on postoperative day (POD) 1, length of stay in ICU, and length of stay in hospital.

Data sources

All clinical data were obtained from electronic patient records and anesthesia records at the hospital, and ICU clinical progress chart.

Statistical analysis

The collected data were summarized and compared in the presence or absence of intravenous acetaminophen. Continuous variables showed medians with interquartile range (IQR) and compared by the Mann–Whitney U test. Categorical variables showed the number of patients and percentages within each group and compared by the Chi-square test or Fisher's exact test.

The outcome of interest as body temperatures were assumed to follow a normal distribution, confirmed by the histogram and the Kolmogorov–Smirnov test. The various body temperatures were summarized as means ± standard deviation and compared between groups by Student's t-test. We depicted a distribution of maximum axillary temperature within 12 h after ICU admission as a violin plot.

We estimated the effect of using acetaminophen on the maximum axillary temperature within 6 and 12 h after ICU admission and confirmed the robustness of our results in three statistical methods: regression, standardization, and inverse probability (IP) weighting. In particular, the estimates obtained from methods standardization and IP weighting are average causal effects, which is the difference between the mean temperature of the entire population with and without acetaminophen using. If the estimates obtained from these methods are similar, the results can be judged to be robust.[12] The common confounders and predictors (both are referred to as covariates) for all methods were selected from a combination of subject-matter knowledge and a directed acyclic graph. Selected confounders were age, sex, body weight, diabetes mellitus, minimally invasive cardiac surgery (MICS), and operation time.[13-19] First, the regression method, multiple linear regression, estimated the effect of acetaminophen by modeling the dependent variable as each outcome and the independent variables as the use of acetaminophen and identified covariates. Second, in the standardization method, we estimated the standardized mean difference. A 95% confidence interval (CI) were calculated using the bootstrap method. Third, in the IP weighting method, we estimated the weighted mean difference using Weight It package in R. This method uses a propensity score (PS).

The PS model was developed using logistic regression, with the dependent variable being the use of acetaminophen and the independent variables being identified covariates. The validity of the PS was confirmed by standardized differences and plot using cobalt package in R.[20]

Statistical significance for all tests was defined by a two-tailed *P* value of <0.05 or by the 95% CI not crossing null. Analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics (version 24.0) software (IBM Japan, Tokyo, Japan).

RESULTS

A total of 321 patients underwent cardiovascular surgery with CPB during the study period, and we analyzed 201 of these patients. Group A and Group N had 101 and 100 patients, respectively. The flow diagram for excluded patients is shown in Figure 1.

Table 1 shows the perioperative characteristics of the study patients. The proportion of female patients and MICS was significantly higher in Group A compared with Group N, while body weight and the dose of intraoperative fentanyl was significantly higher in Group N compared with Group A.

Perioperative body temperature and the incidence of postoperative hyperthermia

Table 2 shows the results of perioperative body temperature and the incidence of postoperative hyperthermia. Figure 2 shows the violin plot in the distribution of maximum axillary temperature within 12 h after ICU admission between two groups. Maximum axillary temperature within 12 h after ICU admission, which is the primary outcome in this study, was significantly lower in Group A compared with Group N. In addition, rectal and esophageal temperatures at the end of surgery, axillary temperature at ICU admission, maximum axillary temperature within 6 h after ICU admission, and axillary temperature at extubation were significantly lower in Group A compared with Group N. The number of body temperature measurements within 12 h after ICU admission was significantly more in Group N.

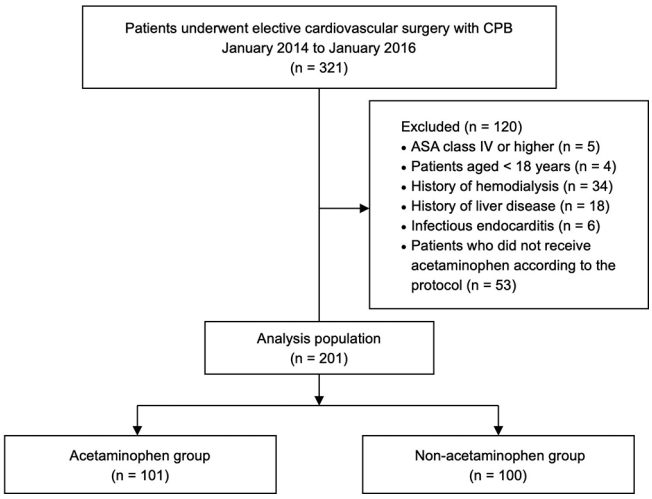

Figure 1: Study flow diagram detailing the selection of patients included in the retrospective analysis. CPB = cardiopulmonary bypass, ASA = American Society of Anesthesiologists

The incidence of hyperthermia within 12 h after ICU admission was significantly lower in Group A compared with Group N. Moreover, the incidence of hyperthermia within 6 h after ICU admission was significantly lower in Group A compared with Group N.

The effects of using acetaminophen on the maximum axillary temperature within 6 and 12 hours after ICU admission

Table 3 shows the effect of using acetaminophen on the maximum body temperature within 12 h after ICU admission for acetaminophen using three statistical methods. The results of the three methods for each outcome were similar, confirming the robustness of the estimated effects. Using acetaminophen lowered body temperature by approximately 0.5°C, which was statistically significant for all methods.

Postoperative clinical course

Supplemental Digital Content 2 shows the postoperative clinical course. Ventilation time in ICU, length of stay in ICU, and length of stay in hospital were significantly shorter in Group A; however, the levels of postoperative inflammatory markers, leukocyte, and CRP on POD 1 did not significantly differ between the groups. The death of a patient did not occur until 90 days after surgery in both groups. There was no obvious adverse event that might have been caused by acetaminophen.

DISCUSSION

In the present study, we investigated the antipyretic effect of intravenous acetaminophen on the body temperature of adult patients after cardiovascular surgery with CPB. Maximum axillary temperature within 12 h after ICU admission was significantly lower in Group A compared with Group N. Moreover, the incidence of hyperthermia within 12 h after ICU admission was significantly lower in Group A compared with Group N. This result indicated that perioperative intravenous acetaminophen inhibits the elevation of body temperature after cardiovascular surgery with CPB.

Table 1: Baseline demographic, surgical characteristics of the study population

Characteristics	Group A (*n*=101)	Group N (*n*=100)	*P*
Age (years)	70 [55, 77]	71 [59, 77]	0.399
Female	53 (52%)	35 (35%)	0.016
Height (cm)	159 [152, 166]	162 [152, 167]	0.312
Body weight (kg)	55.0 [46.1, 64.2]	59.9 [51.4, 68.1]	0.003
NYHA			0.274
Class I	24 (24%)	33 (33%)	
Class II	52 (51%)	49 (49%)	
Class III	25 (25%)	18 (18%)	
LVEF (%)	64 [61, 72]	65 [50, 72]	0.182
Preoperative leucocyte (/μl)	5200 [4500, 6500]	5500 [4500, 6575]	0.825
Preoperative CRP (mg/dl)	0.08 [0.03, 0.25]	0.1 [0.04, 0.32]	0.374
Diabetes mellitus	23 (23%)	32 (32%)	0.157
COPD	4 (4%)	5 (5%)	0.748
Ischemic heart disease	25 (25%)	33 (33%)	0.216
Chronic heart failure	73 (73%)	60 (60%)	0.075
Type of surgery			0.782
CABG	10 (10%)	14 (14%)	
Valve	71 (70%)	64 (64%)	
CABG + Valve	10 (10%)	11 (11%)	
Others*	10 (10%)	11 (11%)	
MICS	43 (43%)	19 (19%)	<0.001
Operation time (min)	273 [235, 337]	304 [244, 385]	0.077
CPB time (min)	132 [107, 166]	130 [108, 188]	0.449
Intraoperative fentanyl (μg/kg)	9.0 [7.5, 10.8]	24.2 [20.0, 30.3]	<0.001

Values are median [inter-quartile range] or number of patients (%). *Others: included following surgeries: aortic replacement or plastic surgery, atrial septal defect closure, tumorectomy, constrictive pericarditis surgery, left ventricular plastic surgery. NYHA=New York Heart Association, LVEF=left ventricular ejection fraction. CRP=C-reactive protein, COPD=chronic obstructive pulmonary disease. CABG=coronary artery bypass grafting, MICS=minimally invasive cardiac surgery. CPB=cardiopulmonary bypass

Table 2: Perioperative body temperature and the incidence of postoperative hyperthermia

Body temperature	Group A (*n*=101)	Group N (*n*=100)	*P*
Before surgery			
Axillary temperature (°C)	36.3±0.3	36.3±0.3	0.469
During surgery			
Minimum rectal temperature (°C)	32.9±2.4	33.2±2.6	0.174
Minimum esophageal temperature (°C)	31.9±3.1	32.3±3.5	0.114
Rectal temperature soon after weaning off CPB (°C)	36.5±0.5	36.6±0.4	0.282
Esophageal temperature soon after weaning off CPB (°C)	37.0±0.5	37.0±0.4	0.357
At the end of surgery			
Rectal temperature (°C)	36.8±0.4	37.0±0.5	<0.001
Esophageal temperature (°C)	36.4±0.5	36.6±0.6	<0.001
At ICU admission			
Axillary temperature (°C)	36.4±0.4	36.5±0.5	0.026
Within 6 h after ICU admission			
Maximum axillary temperature (°C)	37.0±0.5	37.6±0.6	<0.001
Within 12 h after ICU admission			
Maximum axillary temperature (°C)	37.2±0.5	37.8±0.6	<0.001
At extubation in ICU			
Axillary temperature (°C)	36.8±0.5	37.2±0.6	<0.001
Number of measurements within 12 h after ICU admission	6.4±1.3	5.6±1.2	0.006
The incidence of Postoperative hyperthermia			
At ICU admission	1 (1%)	3 (3%)	0.602
Within 6 h after ICU admission	14 (14%)	60 (60%)	<0.001
Within 12 h after ICU admission	27 (27%)	67 (67%)	<0.001

Values are means±standard deviations or number of patients (%). CPB=cardiopulmonary bypass, ICU=intensive care unit

Postoperative hyperthermia is a common complication of cardiovascular surgery with CPB, and numerous studies have demonstrated an association between elevated body temperature and the deterioration in cognitive performance.[6,7,21] Prior to the present study, only one study had reported the antipyretic effect of acetaminophen on postoperative hyperthermia after cardiovascular surgery. Abdollahi and colleagues conducted a randomized placebo-controlled trial to investigate the effect of single preoperative acetaminophen on body temperature during the 24 h following cardiac surgery with CPB.[22] They proved that axillary temperature was significantly lower in the acetaminophen group compared with the control group at 8 and 16 h following the operation. Mean axillary temperature

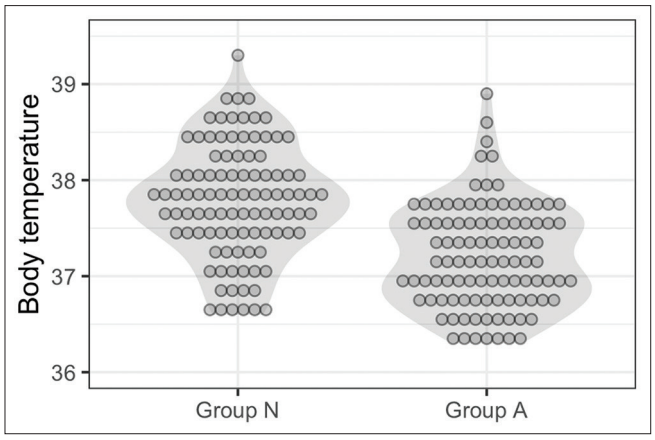

Figure 2: The violin plot in distribution of maximum axillary temperature within 12 h after ICU admission between two groups. ICU = intensive care unit

Table 3: The effects of using Acetaminophen on the maximum axillary temperature within 6 and 12 hours after ICU admission

Methods*	Effect estimates	95% CI	
		Lower limit	Upper limit
Outcome: the maximum axillary temperature within 6 h after ICU admission			
Regression	−0.55	−0.72	−0.38
Standardization	−0.55	−0.69	−0.41
IP weighting	−0.53	−0.69	−0.37
Outcome: the maximum axillary temperature within 12 h after ICU admission			
Regression	−0.54	−0.70	−0.38
Standardization	−0.54	−0.69	−0.39
IP weighting	−0.52	−0.68	−0.36

*Common confounders and predictors in all methods were age, sex, body weight, diabetes mellitus, minimally invasive cardiac surgery (MICS), and operation time. ICU=intensive care unit, CI=confidence interval, IP=Inverse probability

during the first 24 h following the operation was also significantly lower in the acetaminophen group. However, their study was conducted in patients aged 1–12 years, which differed from our study by approximately 70 years. The difference in age influences body temperature. First, febrile response is more persistent in young animals compared with old animals.[23] Second, autonomic thermoregulatory response is reduced in the elderly.[13,14] Third, peripheral body temperature is lower in old people compared with young people.[24] Additionally, adult cardiac surgery is longer and is characterized by longer CPB time compared with pediatric cardiac surgery. Indeed, operation time was longer in the present study (300 min) compared with the previous study (170 min). Degree of invasion is generally related to postoperative hyperthermia.[18] Furthermore, the risk of cerebral ischemia during and after cardiovascular surgery may be higher in old people compared with young people due to age-related arteriosclerosis and the long CPB time. Therefore, the present study provides great value as it is the first to investigate the effect of acetaminophen on postoperative body temperature after cardiovascular surgery with CPB in adult patients.

Previous studies in adult patients reported that the maximum bladder or nasopharyngeal temperature after CPB was 38.0°C to 38.5°C.[3,25] These body temperatures were higher compared with maximum axillary temperature within 12 h after ICU admission in the present study (37.1°C and 37.8°C in group A and group N, respectively). These differences may be a result of the measurement site differences; axillary temperature was classified as peripheral body temperature, while bladder and nasopharyngeal temperatures were classified as core body temperature. In addition, axillary temperature is not a reliable representative of body core temperature and changes based on atmospheric or room temperature and the measurement technique employed.[26] In adults, axillary temperature is approximately 0.6°C lower compared with rectal temperature, and the mean difference between the axillary temperature and rectal temperature in elderly people increases up to 0.9°C.[13,26] Meanwhile, the mean difference between pulmonary artery temperature and axillary temperature during cardiac surgery is 0.2°C.[27] Therefore, it is likely that the difference between core and peripheral body temperatures decreases under sedation. In the present study, maximum axillary temperature within 6 hours after ICU admission for many cases under sedation due to mechanical ventilation was significantly lower in Group A compared with Group N. Additionally, axillary temperature at extubation when all patients were not under sedation was significantly lower in Group A compared with Group N. These data suggest that the antipyretic effect of acetaminophen is favorable after cardiovascular surgery with CPB even when the axillary temperature differs from the core body temperature. However, based on these results, we could not conclude that acetaminophen shifted the inter-threshold range to the normal range.

Our study had all the limitations and potential for bias inherent to retrospective studies. First, based on the start of perioperative intravenous acetaminophen in our hospital, we could not exclude the influence associated with changes in perioperative management. A major change related to perioperative management between the study periods was the intermittent bolus doses of intraoperative fentanyl. Many anesthesiologists used fentanyl to avoid postoperative hemodynamic responses due to pain and thermoregulation, which occurs immediately after the discontinuation of remifentanil. Less fentanyl had been administered after the start of acetaminophen administration, because of its analgesic

and antipyretic effects. Opioids greatly affect the expansion of the inter-threshold range to low-temperature regions, meanwhile having a limited effect on the high-temperature region.[28] Meanwhile, there was the possibility that intraoperative fentanyl in patients undergoing cardiac surgery with CPB increased the inflammatory response concerned with postoperative hyperthermia compared with morphine even though the dose-dependency of the effect is unknown.[29] Therefore, higher dose of intraoperative fentanyl may be a concern of high postoperative body temperature in the non-acetaminophen group compared with the acetaminophen group. For these reasons, although higher dose of intraoperative fentanyl might affect postoperative body temperature, distinguishing the effects of acetaminophen and fentanyl on body temperature was difficult. However, in most patients, fentanyl was not administered after surgery, and it was presumed that the blood concentration of fentanyl was not so high during postoperative periods. Additionally, fentanyl affects the thermoregulatory responses less than other general anesthetics.[28] Therefore, in this study, fentanyl could have little effect on body temperature. Second, axillary temperature after ICU admission was not continuously measured. Consequently, the possibility exists that the true maximum body temperature was missed. Additionally, the temperature was measured at an arbitrary time based on the decision of the nursing staff, and the number of measurements was significantly different between the two groups. Third, this study had a relatively small sample size, was conducted at a single institution, and had many exclusion criteria related to patient background. Therefore, the results obtained may not be applicable to all cases after cardiovascular surgery.

However, the present study is the first organized investigation to demonstrate that perioperative intravenous acetaminophen inhibits the elevation of body temperature after cardiovascular surgery with CPB. To clarify the effectiveness of perioperative acetaminophen after cardiovascular surgery, prospective studies that include continued measurement of core temperature and an assessment of postoperative cognitive functions are warranted.

CONCLUSIONS

Perioperative intravenous acetaminophen inhibited the elevation of body temperature after cardiovascular surgery with CPB, compared with the non-acetaminophen group. Thus, the antipyretic effect of acetaminophen may be beneficial for controlling body temperature in adult patients who undergo cardiovascular surgery with CPB.

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethical Committee of Nagasaki University Hospital (approval No. 17112019; date of approval: 21th November 2017), which follows the Declaration of Helsinki. The ethics committee agreed to waive the written informed consent due to the retrospective nature of the study.

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Conflicts of interest

There are no conflicts of interest.

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Supplemental Digital Content 1: STROBE Statement
Checklist of items that should be included in reports of observational studies

Section/Topic	Item no	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
		Introduction	
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State-specific objectives, including any prespecified hypotheses	4
		Methods	
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Cohort study-Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study-Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study-Give the eligibility criteria, and the sources and methods of selection of participants	5, 6
		(b) Cohort study-For matched studies, give matching criteria and number of exposed and unexposed Case-control study-For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	We determined the sample size from the number of cases in the study period.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7, 8
		(b) Describe any methods used to examine subgroups and interactions	Not applicable
		(c) Explain how missing data were addressed	No missing data
		(d) Cohort study-If applicable, explain how the loss to follow-up was addressed Case-control study-If applicable, explain how matching of cases and controls was addressed Cross-sectional study-If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable

Contd...

Supplemental Digital Content 1: Contd...

Section/Topic	Item no	Recommendation	Reported on Page No
		Results	
Participants	13	(a) Report numbers of individuals at each stage of study-e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	9, Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) Cohort study-Summarise follow-up time (e.g., average and total amount)	Table 2
Outcome data	15	Cohort study-Report numbers of outcome events or summary measures over time	9, 10, Table 2, Supplemental Digital Content 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, Table 3
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done-e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable
		Discussion	
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss the limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13, 14
		Other Information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

Supplemental Digital Content 2: Postoperative clinical course

Postoperative clinical course	Group A (*n*=101)	Group N (*n*=100)	*P*
Ventilation time in ICU (min)	285 [195, 435]	603 [283, 971]	<0.001
Leukocyte on POD 1 (/μl)	9000 [7450, 11600]	8500 [6650, 11150]	0.298
CRP on POD 1 (mg/dl)	6.04 [4.57, 8.11]	6.54 [4.51, 7.91]	0.778
Length of stay in ICU (day)	2 [1, 2]	2 [1, 3]	0.016
Length of stay in hospital (day)	18 [15, 23]	20 [17, 24]	0.016

Values are median [inter-quartile range]. ICU=intensive care unit, POD=postoperative day, CRP=C-reactive protein