A Randomized Study on the Prophylactic Use of Acetaminophen to Prevent Fever after the Removal of Drainage Tubes for Lumbar Surgery

Kaifeng Ye, PhD1,2,3, Yan Li, PhD1,2,3, Yong Xing, PhD1,2,3, Kaixi Liu, PhD4, Fang Zhou, PhD1,2,3, Yun Tian, PhD1,2,3, Yanping Zhang, BS1,2,3

1Department of Orthopedics and 4Anesthesiology Department, Peking University Third Hospital, 2Engineering Research Center of Bone and Joint Precision Medicine, Ministry of Education, Peking University Third Hospital and 3Beijing Key Laboratory of Spinal Disease Research, Peking University Third Hospital, Beijing, China

Background: Many inpatients encounter a fever in the first 24 h after drainage removal. It is costly to exclude the possibility of deep infection and cultures usually fail to identify the etiology. We hypothesize that the fever is caused by a normal inflammatory response and tested whether the prophylactic use of acetaminophen could reduce the fever rate.

Methods: This was a prospectively randomized clinical trial performed from July 2019 to January 2020. A total of 183 consecutive patients undergoing lumbar spine surgery were prospectively randomized into two groups. Ninety-one patients were randomized into the study group; they received oral acetaminophen before removal of the drainage tubes and a second dose at 8 p.m. on the same day. The remaining 92 patients were placed in the control group, and they were given routine treatment without acetaminophen. The two groups were compared for differences in age, sex, height, weight, BMI, surgical segments, surgical time, blood loss, blood transfusion, ASA score, duration of drainage, total volume of the drainage, variation of WBC and CRP, hospital stay after the removal of the drainage tube and the rate of fever. Student’s t-test and the Mann–Whitney U test were used to analyze the continuous data, while the chi-square test was used for the analysis of the ranked data.

Results: Regarding the comparisons of basic information, there were no significant differences between the two groups for age, height, weight, BMI, surgical segments, surgical time, blood loss, blood transfusion, total drainage volume, duration of drainage, hospital stay, WBC, and CRP variation or the duration of hospital stay after removal of the drainage tube (all p > 0.05). However, the fever rate was significantly different (p = 0.006), and the fever rate of the study group (14/91, 15.38%) was significantly lower than that of the control group (30/92, 32.61%). In the study group, there were no complications related to the use of acetaminophen during the hospital stay or during the outpatient follow-up period.

Conclusion: Fever after removal of tube drainage is caused by a normal inflammatory response, and a small dose of acetaminophen could significantly reduce the possibility of fever.

Key words: Acetaminophen; Fever; Inflammatory response; Lumbar drainage; Prostaglandin
When these fevers appeared, we performed many laboratory tests to exclude the possibility of deep infection but failed to confirm the etiology of the fever in most cases. The rate of surgical site infection has been reported to range from 0.7% to 12%, and the rate in our hospital was approximately 0.1%. If an infection occurred, it would be difficult for a patient to recover. Fortunately, almost all of the patients’ temperatures gradually became normal after observation or antipyretic treatments before discharge. Similar to the reports of many previous studies, the evaluation of these fevers was costly and time-consuming, and they made the patients uncomfortable and could increase their medical expenditures, prolong their hospital stay and waste healthcare resources.

To address this challenging issue, we carried out a thorough literature review. To the best of our knowledge, no previous research has focused on fever after the removal of drainage tubes. However, we found that many studies paid attention to early postoperative fever and suggested that the main reason for postoperative fever was the inflammatory response due to tissue trauma during surgery. Inflammation is a normal physiological reaction during the process of healing, and the extent of tissue trauma correlates with the possibility of fever. Many previous studies have further proven that the main inflammatory responses are due to pyrogenic cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-gamma. These mediators act directly on the preoptic area of the hypothalamus and cause a release of pyrogens, which could raise the thermoregulatory “set point” for the body temperature and cause fever.

Furthermore, a previous investigation indicated that the presence of hematoma appeared to be a relatively common cause of fever. In addition, many studies have discovered a high concentration of IL-6 in the drained fluid after surgery. Therefore, we infer that once the drainage tube is removed from lumbar patients after surgery, the pyrogenic cytokines cannot flow outside of the surgical area and then accumulate gradually. A small hematoma forms, and the cytokines can ooze into the circulatory system to cause a fever. If we use acetylsalicylic acid to counteract the effects of prostaglandins in advance and then block the production of prostaglandins, perhaps we can lower the possibility of fever when the drainage tube is removed.

The aims of this prospective, randomized study were (1) to determine the efficacy of the prophylactic use of acetylsalicylic acid before lumbar drainage tube removal to prevent fever and (2) to identify whether fever was associated with age and sex. We hypothesized that the preventive use of acetylsalicylic acid could reduce the possibility of fever after the removal of drainage tubes from surgical lumbar disease patients.

Study Design and Patients
We performed a single-blinded randomized controlled trial (NCT04042948) in the Department of Orthopaedics at our hospital from July 2019 to January 2020, and the first registration day was August 2, 2019. Approval was obtained from the Ethics Committee of our hospital, and the approval number was LM2019142.

Patients who underwent lumbar operations in our hospital were recruited. We calculated the sample size with a 5% significance level and 80% power, and 78 patients per group were necessary. We finally decided to recruit 95 patients in each group to allow for dropouts. The patients were randomly divided into two groups using a computer-generated random number list: the study group and the control group. The patients in the study group received an acetaminophen pill (Tylenol, 650 mg) before the removal of the lumbar drainage tube, and another pill was administered at 8 p.m. on the same day, while the patients in the control group did not receive acetaminophen. In this study, we required the time of drainage tube removal to be from 8 a.m. to 10 a.m. in the morning to ensure that the first dose of acetaminophen was taken in the morning.

The inclusion criteria were as follows: (1) adult patients conscious enough to provide informed consent; (2) a clear diagnosis of degenerative lumbar spinal disease; (3) one to two surgical segments; (4) indwelling drainage tube after the operation; and (5) normal hepatic and renal function. The exclusion criteria were as follows: (1) age <18 years; (2) more than two surgical segments; (3) abnormal hepatic and renal function; and (4) a history of stomach disease.

Protocol
All of the included patients signed the informed consent form on the day before the surgery, and the first group of researchers checked the computer-generated random number list, divided the patients into their corresponding groups and informed the second and third groups of researchers. The second and third groups were blinded to the patients’ allocation before receiving information from the first group. The first group was blinded to all of the clinical information about the patients postoperatively.

All operations were performed under general anesthesia by senior spine surgeons and fluoroscopy control on a radiolucent operation table. The extent of the surgery depended on the severity of the disease, and all of the patients had a closed wound drain placed below the deep fascia over the exposed dura before wound closure. No complications occurred during the operations.

All patients received routine treatment and care before the drainage tubes were removed. Our nurses recorded the patients’ temperatures four times a day and the volume of the drainage collections once a day. All of the data were uploaded to the medical system. When the recorded drainage volume over 24 h was below 50 mL, the attending physician decided to remove the drainage tube. All patients underwent laboratory tests for the concentrations of white blood cells (WBCs) and C-reactive protein (CRP) the day after drainage tube removal. For the study group, the extra intervention was a pill of acetaminophen taken before the removal of the drainage tube and another pill taken orally at 8 p.m.
**Fig. 1** The process of the study

**TABLE 1** The characteristics of the two groups expressed as continuous data

| Characteristic                  | Study group Mean (SD) | Control group Mean (SD) | Total Mean (SD) | t/Z   | p value |
|---------------------------------|-----------------------|-------------------------|----------------|-------|---------|
| Age (year)                      | 50.76 (11.70)         | 51.91 (12.12)           | 51.34 (11.89)  | −0.809| 0.419   |
| Height (cm)                     | 164.79 (8.39)         | 166.26 (8.27)           | 165.53 (8.34)  | −1.199| 0.230   |
| Weight (kg)*                    | 69.34 (11.34)         | 70.25 (10.31)           | 69.80 (10.81)  | 0.568*| 0.571   |
| BMI (kg/m²)                     | 25.52 (3.67)          | 25.39 (3.01)            | 25.46 (3.35)   | −0.054| 0.957   |
| Surgical segments               | 1.29 (0.48)           | 1.35 (0.55)             | 1.32 (0.51)    | −0.726| 0.468   |
| Surgical time (min)             | 124.44 (37.17)        | 121.81 (39.24)          | 123.19 (38.07) | −0.454| 0.649   |
| Blood loss (ml)                 | 246.39 (143.23)       | 266.00 (145.62)         | 256.19 (144.36)| −1.023| 0.307   |
| Blood transfusion (ml)          | 90.83                 | 109.24                  | 99.46          | −1.804| 0.071   |
| Total drainage volume (ml)      | 481.43 (302.60)       | 454.99 (324.47)         | 468.21 (313.13)| −0.837| 0.402   |
| Duration of drainage (day)      | 3.36 (1.01)           | 3.30 (0.91)             | 3.33 (0.96)    | −0.167| 0.867   |
| Hospital stay (day)             | 7.68 (1.93)           | 8.12 (2.71)             | 7.91 (2.36)    | −0.647| 0.517   |
| WBC (>10^9/L)                   | 8.25 (2.68)           | 8.69 (2.78)             | 8.47 (2.73)    | −1.165| 0.244   |
| CRP (mg/dL)                     | 3.77 (3.61)           | 4.09 (3.58)             | 3.93 (3.58)    | −0.837| 0.402   |
| Duration of hospital stay after removal of the drainage tube (day) | 2.23 (1.42) | 2.82 (2.61) | 2.52 (2.12) | −1.438| 0.151   |

* Student’s t-test and the rest were Mann–Whitney U test.; * The t value and the rest were Z value.
Our nurse team kept recording the patients' temperatures four times a day and uploading the data to the medical system. The upper limit of a normal temperature was 37.7°C, so a temperature >37.8°C at any time within the first 24 h after the removal of the drainage tube indicated that a fever had developed.

**Data and Observation**

All of the patients' basic clinical information was collected, including age, sex, height, weight, body mass index (BMI), surgical segments, surgical time, blood loss, blood transfusion, American Society of Anesthesiologists (ASA) score, duration of drainage tube use, and total drainage volume.

| Characteristic | Study group | Control group |
|----------------|-------------|---------------|
| Age            | 0.001       | 0.004         |
| Height         | 0.020       | 0.206         |
| Weight         | 0.620       | 0.213         |
| BMI            | 0.039       | 0.118         |
| Surgical segments | 0.000    | 0.000         |
| Surgical time  | 0.006       | 0.000         |
| Blood loss     | 0.000       | 0.000         |
| Blood transfusion | 0.000    | 0.000         |
| Total drainage volume | 0.006  | 0.000         |
| Duration of drainage | 0.000  | 0.000         |
| Duration of hospital stay | 0.000  | 0.000         |
| WBC            | 0.000       | 0.000         |
| CRP            | 0.000       | 0.000         |
| Duration of hospital stay after removal of the drainage tube | 0.000 | 0.000 |

TABLE 2 The Shapiro–Wilk test for normality of the continuous data (p > 0.05 suggests that the data were normally distributed)

| Characteristic | Study group | Control group |
|----------------|-------------|---------------|
| Age            | 0.010       | 0.004         |
| Height         | 0.020       | 0.206         |
| Weight         | 0.620       | 0.213         |
| BMI            | 0.039       | 0.118         |
| Surgical segments | 0.000    | 0.000         |
| Surgical time  | 0.006       | 0.000         |
| Blood loss     | 0.000       | 0.000         |
| Blood transfusion | 0.000    | 0.000         |
| Total drainage volume | 0.006  | 0.000         |
| Duration of drainage | 0.000  | 0.000         |
| Duration of hospital stay | 0.000  | 0.000         |
| WBC            | 0.000       | 0.000         |
| CRP            | 0.000       | 0.000         |
| Duration of hospital stay after removal of the drainage tube | 0.000 | 0.000 |

The main observation index was temperature within the first 24 h after the drainage tube was removed. Once a fever developed, the data collection for that patient ended. The attending physicians started the diagnostic workups depending on the medical history and conducted a physical examination to identify the etiology of the fever. The possible workups included chest X-ray, urinalysis, urine culture, and blood culture. The other observation indices were the variations in WBC and CRP levels, the length of hospital stay after the removal of the drainage tube to discharge, and the whole hospital stay.

We compared the above data of the two groups to identify the efficacy of the prophylactic use of acetaminophen for preventing fever. Furthermore, we conducted subgroup analysis in the study and control groups to identify the role of age and sex in fever.

**Statistical Analysis**

A descriptive analysis was performed of the main study variables. All continuous data were tested for normality with the Shapiro–Wilk test. If the data were normally distributed, Student’s t-test was used for the analysis. The Mann–Whitney U test was performed for nonnormally distributed data. For ranked data, the chi-square test was used for analysis. The value of p < 0.05 was considered statistically significant. All analyses were performed with SPSS Statistics (version 24.0; IBM Corp., Armonk, NY, USA).

**Results**

**Comprehensive Description**

The study process is shown in Fig. 1. In total, 190 patients participated in this research, and seven patients were excluded because they refused the operation (six patients) or underwent reoperation for postoperative hematoma (one...
Finally, the study comprised 183 patients; 91 patients were in the study group, and the rest were in the control group. For the main diagnosis of these patients, there were 129 with lumbar spinal stenosis, 35 with lumbar spondylolisthesis, and 19 with lumbar disc herniations.

There were 80 male and 103 female patients, and the average age was 51.34 years. The average weight was 69.80 kg, and the average height was 165.53 cm, equivalent to an average BMI of 25.46 kg/m². The basic characteristics of the patients are listed in Table 1.

**Comparisons of the Study and Control Groups**

The Shapiro–Wilk (Table 2) test showed that other than weight, the remaining continuous data were nonnormally distributed ($p < 0.05$), so we analyzed them with the Mann–Whitney $U$ test, while the weight data were tested by Student’s $t$-test. The comparison of the basic data is displayed in Tables 1 and 3. We determined that there were no differences in age, sex, height, weight, BMI, surgical segments, surgical time, blood loss, transfusion, ASA score, duration of drainage tube use, or total drainage volume between the two groups ($p > 0.05$). Although the levels of WBC and CRP were lower, the length of hospital stay and the length of hospital stay after the removal of the drainage tube were shorter in the study group than in the control group, but the differences were not significant ($p > 0.05$). However, the rate of fever was significantly different ($p = 0.006$), and the study group (14/91, 15.38%) had a significantly lower rate of fever than the control group (30/92, 32.61%).

**Subgroup Comparisons**

We divided the study group and control group into subgroups according to the condition of fever and determined...
that regardless of the group, the age and sex had no significant differences between the groups, suggesting that fever was not associated with age or sex (Table 4).

**Outcomes**

Among the cases of fever, there were three positive urinary cultures, one in the study group (*Escherichia coli*) and two in the control group (*Acinetobacter junii* and coagulase negative staphylococcus), which were treated by antibiotics depending on the results of the drug sensitivity test. Additionally, two patients with fever were experiencing cerebrospinal fluid leakage (discovered after the postoperative observation of fever). During follow-up in the outpatient department, no infections were discovered after discharge. In the study group, there were no complications related to the use of acetaminophen during the hospital stay or the outpatient follow-up period.

**Discussion**

Similar to postoperative fever, fever after the removal of a drainage tube is always a challenge for doctors. Diagnostic workups for fever could be costly, waste time, and prolong the hospital stay of patients. Moreover, most of the evaluations fail to identify the cause of the fever. In this study, we used acetaminophen (Tylenol) as a prophylactic treatment for fever after the removal of drainage tubes for lumbar surgery, and the results showed that this approach could significantly reduce the possibility of fever.

To the best of our knowledge, our research is the first to focus on the problem of fever after the removal of a drainage tube placed during lumbar surgery. Many previous studies have focused on postoperative fever. The most consistent conclusion is that this fever is a physiological response due to the damage caused by surgical trauma, and the degree of fever is correlated with the extent of tissue trauma during surgery.\(^4,10,15,17\) The inflammatory reaction stimulated by tissue trauma could trigger the release of cytokines such as IL1, IL6, and TNF-\(\alpha\) in the local surgical area, and the released cytokines act as endogenous pyrogens to stimulate the preoptic area of the hypothalamus to increase prostaglandin production, raising the thermoregulatory set point for body temperature.\(^11,17,18,23,24\) Based on these theories, we proposed that when the drainage tube was removed, the local inflammatory cytokines could not flow out, and then a small hematoma formed. With the increase in pressure caused by the hematoma and the increased local concentration of cytokines, the inflammatory cytokines could enter the systemic circulation and then raise the body temperature.\(^11,17,18,23,24\) Based on these theories, we proposed that when the drainage tube was removed, the local inflammatory cytokines could not flow out, and then a small hematoma formed. With the increase in pressure caused by the hematoma and the increased local concentration of cytokines, the inflammatory cytokines could enter the systemic circulation and then raise the body temperature (Figs. 2 and 3). Therefore, if we use acetaminophen in advance to depress the function of prostaglandins (Fig. 4), we could lower the possibility of fever when the drainage tube is removed. The results of the study proved our hypothesis.

Many previous studies directly or indirectly support our proposal. The reports of Chmel et al.\(^25\) and Gemer et al.\(^26\) both suggested that hematoma at the wound site was the source of fever, which is in line with our thoughts. Many previous studies have noted that postoperative drainage fluid...
is rich in inflammatory cytokines such as IL1, IL6, and TNF-a, and the levels of these cytokines are higher in fever patients. Mark et al. and Gideon et al. both compared the fever rate of patients with or without drainage tubes postoperatively and declared that patients without postoperative drainage were more vulnerable to fever. More interestingly, based on Hao’s research, we found that if the drainage tube is intermittently clamped after lumbar surgery, the patient was more likely to develop a fever. All of the above conclusions could support our original idea that the removal of the drainage tube could stop the outflow of inflammatory cytokines and then cause fever.

Tylenol, a brand of acetaminophen, is a common analgesic-antipyretic medicine applied in our clinical treatment. This drug could inhibit prostaglandin synthase in the hypothalamic thermoregulation center and then reduce the production of prostaglandin. Based on what we discussed above, when the drainage tube is removed, the elevated cytokines could act on the hypothalamic thermoregulation center and cause a fever. The prophylactic acetaminophen could depress the activity of prostaglandin synthase to fight against stimulation from the cytokines and reduce the possibility of fever. The half-life of Tylenol is approximately 2 h, so the serum concentration of acetaminophen after the evening dose would be too low to have an antipyretic effect the next day. It was thus not necessary to worry if the use of acetaminophen would mask any signs of infection, and the number of infectious cases in the study group could prove this.

The concentrations of WBCs and CRP were not significantly different between groups in this study. As we observed, acetaminophen could only depress the activity of prostaglandin synthase but not suppress the inflammatory reaction caused by surgical trauma, so it was reasonable to observe this result. The length of hospital stay after drainage removal in the study group was shorter than that of the control group (2.23 days vs 2.82 days), but the difference was not significant because some patients asked to delay their discharge until the weekend or based on their personal condition. Roughly consistent with Zhu’s study, the control of fever after surgery could shorten the hospital stay.

Our study had some limitations. First, this was not a triple-blinded study. Second, due to limited funding, we did not directly test the changes in the concentrations of cytokines in response to the acetaminophen before and after the drainage tube was removed. However, we are the first to focus on fever after the removal of drainage tubes for lumbar surgery, and our research proved that prophylactic treatment with acetaminophen could significantly lower the potential for developing fever.

**Conclusion**

Fever after the removal of drainage tubes is caused by a normal inflammatory response, which is not associated with age or sex. After removal of the drainage tube from surgical lumbar patients, a small dose of acetaminophen could significantly reduce the possibility of fever. This approach could improve patient comfort, reduce the waste of medical resources, and speed up the discharge of patients. In our future research, we will try to determine the risk factors for fever after drainage tube removal and narrow the scope of patients who should receive prophylactic medicine.

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**Conflict of Interest**

There is no conflict of interest.

**Authors’ Contributions**

Kaifeng Ye and Yan Li collected data and wrote the article; Yong Xing was responsible for the literature review and the distribution of the patients; Kaixi Liu drew the illustrations; Fang Zhou, Yanping Zhang, and Yun Tian designed the study. All authors read and approved the final manuscript.

**Availability of Data and Materials**

All data and materials used to support the findings of this study are included within the article.

**Ethics Approval and Consent to Participate**

All procedures performed in this study were conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The Ethics Committee of Peking University Third Hospital approved this study. Each author certifies that all investigations were conducted in conformity with ethical principles. All participants provided informed consent before their participation in the study.

**Consent for Publication**

All authors agreed to publish “A randomized study on the prophylactic use of acetaminophen to prevent fever after the removal of drainage tubes for lumbar surgery” in *Orthopaedic Surgery*. We have received written consent from the participants to publish their clinical data (just anonymized clinical data without any identifying images or information).

**Competing Interests**

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.
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