Effect of temperature maintenance by forced-air warming blankets of different temperatures on changes in inflammatory factors in children undergoing congenital hip dislocation surgery

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Abstract

Background: Hypothermia is associated with many adverse clinical outcomes in pediatric patients, and thus, it is important to find an effective and safe method for preventing peri-operative hypothermia and its associated adverse outcomes in pediatric patients. This study aimed to investigate the effect of forced-air warming blankets with different temperatures on changes in the transforming growth factor-β (TGF-β), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 levels in children undergoing surgical treatment for developmental displacement of the hip (DDH).

Methods: The study included 123 children undergoing surgery for DDH under general anesthesia. The patients were randomly assigned to three groups, using a random number table: the 32, 38, and 43°C groups according to the temperature setting of the forced-air warming blankets. For each patient, body temperature was recorded immediately after anesthesia induction and intubation (T_0), at initial incision (T_1), at 1 h after incision (T_2), at 2 h after incision (T_3), at the end of surgery (T_4), immediately upon return to the ward after surgery (T_5), and then at 12 h (T_6), 24 h (T_7), 36 h (T_8), and 48 h (T_9) after the surgery. The serum levels of TGF-β, TNF-α, IL-1β, and IL-10 were measured at T_0 and T_4 for all groups.

Results: The number of patients with fever in the 38°C group was significantly less than those in the 32 and 43°C groups ($\chi^2 = 6.630$, $P = 0.036$). At T_0, the body temperatures in the 38 and 43°C groups were significantly higher than that in the 32°C group ($F = 17.992$, $P < 0.001$). At T_2, the body temperature was significantly higher in the 43°C group than those in the 32 and 38°C groups ($F = 12.776$, $P < 0.001$). Moreover, at T_4, the serum levels of TGF-β ($F = 3286.548$, $P < 0.001$) and IL-10 ($F = 4628.983$, $P < 0.001$) were significantly increased in the 38°C group, and the serum levels of TNF-α ($F = 911.415$, $P < 0.001$) and IL-1β ($F = 322.191$, $P < 0.001$) were significantly decreased in the 38°C group, compared with the levels in the 32 and 43°C groups.

Conclusion: Force-air warming blankets set at 38°C maintained stable body temperature with less adverse outcome and effectively inhibited the inflammatory response in pediatric patients undergoing surgery for DDH.

Clinical trial registration: ChiCTR1800014820; http://www.chictr.org.cn/showproj.aspx?proj=25240.

Keywords: Body temperature; Developmental displacement of the hip; Inflammatory factor; Rehabilitation; Transforming growth factor-beta

Introduction

Hypothermia, defined as a core temperature <36.7°C, frequently occurs in the peri-operative period, especially in infants and young children. Peri-operative hypothermia can be caused by a large surgical wound, great blood loss, long operative time, disrupted thermoregulation by anesthesia, and use of low-temperature fluids. Hypothermia is associated with many adverse clinical outcomes, such as infection, cardiovascular complications, increased length of hospital stay, metabolic dysfunction, and even death.[1] Therefore, it is important to find an effective and safe method for preventing peri-operative hypothermia and its associated adverse outcomes in pediatric patients.

Developmental displacement of the hip (DDH) is a common pediatric malformation characterized by displacement of the femoral head. Orthopedic surgery has been found to be effective and safe for the treatment of DDH in infants and young children.[2] Pediatric patients who undergo surgical treatment for DDH are prone to peri-operative hypothermia due to the large surgical wound and long operative time.[3] Forced-air warming is recognized as the most effective intra-operative thermal

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000846

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Chinese Medical Journal 2020;133(15)

Received: 28-01-2020 **Edited by:** Li-Shao Guo

insulation method to prevent peri-operative hypothermia, and the recommended temperature for adult patients is 32 to 38°C.[4,5] However, few studies have investigated the efficacy of forced-air warming at different temperatures in pediatric patients undergoing surgery to correct congenital hip dislocation.

Additionally, it has been reported that appropriate peri-operative thermal insulation can effectively inhibit systemic inflammatory responses in children.[6] Our previous study showed that intra-operative thermal insulation can also effectively suppress stress-induced inflammation, thus improving the child's prognosis.[7] Moreover, Murata *et al*[8] reported that changes in body temperature can affect activation of the transforming growth factor-β (TGF-β) signaling pathway, an anti-inflammatory cytokine pathway that regulates cell growth and differentiation.[9] However, the effect of the temperature set by the forced-air warming device on the levels of TGF-β and other inflammatory factors remains unclear.

In the present study, we aimed to determine the effect of forced-air warming blankets set at different thermal insulation temperatures on the changes in body temperature and serum levels of TGF-β and other inflammatory factors in pediatric patients undergoing surgical correction of congenital hip dislocation.

Methods

Ethical approval

The Ethics Committee of the Guangzhou Women and Children's Medical Center approved this study (No. 2017121407). The patients' parents gave their informed consent before patients' inclusion in the study.

Patients

This study included 123 children with DDH who underwent orthopedic surgery under general anesthesia. Inclusion criteria were as follows: age ranged from 2 to 7 years old; American Society of Anesthesiologists (ASA)-physical status I–II according to the ASA Physical Status Classification[10]; and no pre-operative respiratory infection, and no abnormalities in routine blood and urine tests. The exclusion criteria were as follows: (1) pre-operative fever of unknown cause; (2) coagulation dysfunction; (3) congenital heart disease; (4) epilepsy; (5) communication or mental retardation; (6) developmental delay, obesity; (7) hypersensitivity to known drugs; (8) severe liver and kidney dysfunction; or (9) severe genetic and metabolic disease. All surgeries were performed by the same group of orthopedic surgeons, using the same surgical procedures.

Among these patients, some cases received acetabular osteotomy or femoral shortening, while others received acetabular osteotomy + femoral shortening. The surgical procedures were carried out according to textbook instructions.[11] Five to six layers of Cellacast Active Cast (Lohmann & Rauscher Internation Gmbh & Co., KG D-56579 Rengsdorf, Germany), which is made of polyester, were applied for all patients. To avoid the influence of surgery method on the results, patients were randomly assigned to three groups, using a random number table: the 32°C group ($n = 42$), the 38°C group ($n = 42$), and the 43°C group ($n = 39$). The intra-operative body temperature of patients in the 32, 38, and the 43°C groups was maintained using a disposable aseptic air heating blanket (model number: 700, Bair Hugger™ Company; St. Paul, Minnesota, USA) with the temperature set to 32, 38, or 43°C, respectively. The temperatures used in this study are safely used in the clinic. The heating blanket covered the entire body except for the operative site. Air was inflated into the blanket for heat insulation, and the temperature was set to 32, 38, or 43°C for children in the 32, 38, and 43°C groups, respectively. To prevent the effect of environmental changes on body temperature, the temperature of the operating room was adjusted to 23°C with a relative humidity of 40% to 50%.

Anesthesia and surgical procedures

All children were fasted for 4 to 8 h, and oral fluids were restricted for 3 to 6 h before surgery. Anesthesia was induced with intravenous injections of fentanyl, propofol, and rocuronium. After successful intubation, the endotracheal tube was fixed and connected to the anesthesia machine for mechanical ventilation, with a tidal volume of 8 to 12 mL/kg, a respiration frequency of 18 to 22 times/min, and an inspiration and expiration ratio of 1:1.5. After induction of anesthesia, central vena catheterization was performed through the right jugular vein and used for hydration and monitoring of venous pressure. After catheterization, the child was placed in a lateral position, and the operative site was disinfected. Anesthesia was maintained using inhalation of 1.5% to 2.5% sevoflurane, intravenous injection of remifentanil by a syringe pump with an initial rate of 0.2 μg/kg per min, and intermittent intravenous injection of vecuronium bromide for muscle relaxation. All the children were monitored with bispectral index and end-tidal carbon dioxide ($ETCO_2$) at the end of expiration. The anesthesia depth was maintained between 40 and 60 during the operation. Respiratory parameters were adjusted to maintain $ETCO_2$ at the end of expiration of 35 to 45 cm H_2O. Real-time monitoring of direct arterial pressure and heart rate was performed to maintain the heart rate and blood pressure within 30% of the baseline values. After the operation, the endotracheal tube was removed once the children recovered autonomous respiration.

Clinical data collection

For each patient, the body temperature recorded immediately after anesthesia induction and intubation (T_0), at initial incision (T_1), at 1 h after incision (T_2), at 2 h after incision (T_3), at the end of surgery (T_4), immediately upon return to the ward after surgery (T_5), and then at 12 h (T_6), 24 h (T_7), 36 h (T_8), and 48 h (T_9) after the surgery. A body temperature probe was placed in the esophagus to measure the body temperature. The operative time, intra-operative blood loss, and intra-operative infusion volume were recorded during surgery. Post-operative fever (defined by axillary temperature above 37.4°C and fluctuation >1°C within 1 day), hospitalization days, and wound infection (defined by the presence of exudation, rupture, and

suppuration of the incision under direct vision during dressing change) were noted. The body temperature at each time point was the main outcome index.

Western blotting

Venous blood (2 mL) was taken from each patient at T_0 and T_4. Blood samples were centrifuged at 4°C, and the serum was removed. Membranes were incubated with primary antibodies against TGF-β (sc-133216; rabbit anti-human TGF-β antibodies, dilution l:5000, Santa Cruz Biotechnology, Dallas, Texas, USA) at 4°C overnight. glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a loading control. Membranes were then incubated with horseradish peroxidase-linked goat anti-rabbit secondary antibodies (1:3000, Santa Cruz Biotechnology) at 37°C for l h. Bands were visualized using a chemiluminescence detection system. The relative expression of TGF-β was normalized to GAPDH expression.

Enzyme-linked immunosorbent assay (ELISA) analysis

The serum levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 were determined by ELISA (Wuhan BOSTER, China). Briefly, 2 mL of venous blood was taken at T_0 and T_4. The blood samples were centrifuged at 4°C, and the supernatant was removed and analyzed using an ELISA kit according to the manufacturer's instructions. The absorbance value was measured using an iMark ELISA device (model: iMark, Bio-Rad Company, Hercules, California, USA) at the wavelength of 490 nm.

Primary and secondary outcome measures

The primary outcome measure was the body temperature at each time point. The secondary outcome measure was the inflammatory factors in T_0 and T_4. Both primary and secondary outcome measures were recorded by a researcher blinded to the experimental conditions.

Sample size determination

The formula used to determine the number of samples compared by multiple sample rates was:

$$n = \frac{2\lambda}{(2\sin^{-1}\sqrt{P_{\max}} - 2\sin^{-1}\sqrt{P_{min}})^2}$$

Where $a = 0.05$ and $\beta = 0.1$, and $P_{\max}$ and $P_{\min}$ are the maximum rate and the minimum rate, respectively. According to literature reports, with $P_{\max} = 0.27$, $P_{\min} = 0.02$, and $\lambda_{a,\beta,k-1} = \lambda_{0.05,0.10,2} = 12.65$ substituted into the formula above, $n = 39$ can be obtained. Thus, a total of 117 cases were needed in the three groups.

Statistical analysis

Statistical analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as the mean and standard deviation of the normal distribution. One-way analysis of variance was used to compare the difference among groups followed by *post-hoc* least significant difference method. Categorical data were analyzed using the Chi-square test. $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of patients

Table 1 summarizes the clinical characteristics of patients in the 32, 38, and 43°C groups. There were no statistically significant differences in age, body weight, gender ratio, operative time, intra-operative blood loss, intra-operative rehydration, post-operative hospitalization days, and wound infection among the three groups ($P > 0.05$). The number of patients with fever in the 38°C group was significantly less than those in the 32 and 43°C groups ($\chi^2 = 6.630$, $P = 0.036$).

Table 1: Clinical characteristics of 123 children undergoing surgery for developmental displacement of the hip under general anesthesia in the three groups.

Items	32°C group ($n = 42$)	38°C group ($n = 42$)	43°C group ($n = 39$)	F/χ^2	P
Age (years)	4.76 ± 1.72	5.38 ± 2.26	4.92 ± 2.92	0.789*	0.454
Body weight (kg)	13.32 ± 4.30	14.41 ± 4.39	14.01 ± 5.72	0.552*	0.579
Gender ratio (male/female)	9/33	10/32	8/31	0.138†	0.933
Operative time (min)	235.00 (106.25)	244.00 (103.00)	220.00 (143.00)	1.855*	0.395
Intra-operative blood loss (mL)	231.50 (207.25)	189.00 (207.75)	231.00 (193.00)	1.989*	0.370
Intra-operative rehydration (mL)	904.50 (560.50)	931.50 (534.50)	1004.00 (619.00)	0.921*	0.631
Fever (n)	7	1	8	6.630†	0.036
Post-operative hospitalization days (days)	3.41 ± 0.90	3.79 ± 1.21	3.72 ± 1.11	1.460*	0.236
Wound infection (n)	0	0	0	0.000†	1.000
Chills (n)	2	2	1	0.358†	0.836
Acetabular osteotomy (n)	21	22	20	0.048†	0.976
Femoral shortening (n)	1	1	1	0.004†	0.998
Acetabular osteotomy + femoral shortening (n)	20	19	18	0.049†	0.976
Extubation time (min)	21.32 ± 1.82	22.08 ± 2.15	21.63 ± 1.99	1.545*	0.217
Awaking time (min)	74.39 ± 5.84	74.20 ± 6.13	75.17 ± 5.93	0.301*	0.744

Data are expressed as mean ± standard deviation or median (interquartile range). * F value. † χ^2 value.

Body temperature

Within each group, the body temperature of patients was significantly increased at T_1 to T_4 compared with that at T_0 and remained within the normal range [Figure 1A], suggesting that the heating temperatures of 32, 38, and 43°C prevented hypothermia during the operation. At T_0, the body temperatures in the 38 and 43°C groups were significantly higher than that in the 32°C group ($F = 17.992$, $P < 0.001$). At T_2, the body temperature was significantly higher in the 43°C group than in the 32 and 38°C groups ($F = 12.776$, $P < 0.001$). At T_4, the body temperature appeared higher in the 38°C group than in the 32 and 43°C groups, although no significant difference was found. Furthermore, within each group, the body temperature was not significantly different among different time points, and at T_5 to T_9 each time point, the body temperature was not significantly different among the three groups ($P > 0.05$) [Figure 1B].

Serum levels of inflammatory factors

We examined the serum levels of TGF-β, TNF-α, IL-1β, and IL-10 at T_0 and T_4 in the 32, 38, and 43°C groups. At T_0, there were no statistically significant differences in the serum levels TGF-β ($F = 2.943$, $P = 0.057$), TNF-α ($F = 2.381$, $P = 0.097$), IL-1β ($F = 1.862$, $P = 0.161$), and IL-10 ($F = 2.459$, $P = 0.090$) among the three groups [Figure 2]. At T_4, the serum levels of TGF-β ($F = 3286.548$, $P < 0.001$) and IL-10 ($F = 4628.983$, $P < 0.001$) were significantly increased in the 38°C group, and the serum levels of TNF-α ($F = 911.415$, $P < 0.001$) and IL-1β ($F = 322.191$, $P < 0.001$) were significantly decreased in the 38°C group, compared with the levels in the 32 and 43°C groups [Figure 2].

Discussion

In this study, we investigated the effect of different temperatures set by forced-air warming blankets on changes in body temperature and the serum levels of inflammatory factors in pediatric patients undergoing surgery for DDH. We found that the temperature of 38°C was best for maintaining stable body temperature with fewer adverse post-operative outcomes. In addition, compared with those in the 32 and 43°C groups, the serum levels of TGF-β and IL-10 were significantly increased, and the serum levels of TNF-α and IL-1β were significantly decreased in the 38°C group. Our findings suggest that a forced-air warming blanket should be set at the temperature of 38°C to reduce hypothermia in pediatric patients undergoing surgery for DDH.

The incidence of intra-operative hypothermia is 43.9% for hip arthroplasty.[12] Frisch *et al*[13] retrospectively reviewed clinical data derived from 1541 patients with hip fracture and found that the risk of deep surgical-site infection was increased in patients who developed hypothermia. Surgical correction of pediatric DDH can cause post-operative hypothermia due to the large exposed body surface; extensive bleeding from the bone, muscle, and other tissues; great intra-operative blood loss; relatively large rehydration volume; long operative duration; and large internal exposure area in the operative field.[14] Accordingly, special attention to pediatric temperature management is required during hip dislocation surgery. Previous research indicated that the risk of hypothermia can be decreased in patients by elevating the ambient temperature to 26°C[15] and suggested that control of the temperature in the operation room might be the most efficient strategy for maintaining the body temperature of children. In this study, we found that forced-air warming blankets set at 32, 38, or 43°C maintained the body temperature in a normal range during the entire operation in children undergoing surgery for DDH. The 32, 38, and 43°C temperature management temperatures selected in this study were chosen based on the three gears provided by the inflatable heating blanket. However, compared with that in the 32°C group, the body temperature was more stable in the 38°C group [Figure 1], which is consistent with the report by Ge *et al*[16] for abdominal surgery. Compared with that in the 38°C group, the body temperature in the 43°C group increased rapidly at T_2 and T_3 and then decreased more quickly to a level below that in the 38°C group at T_4. The lower body

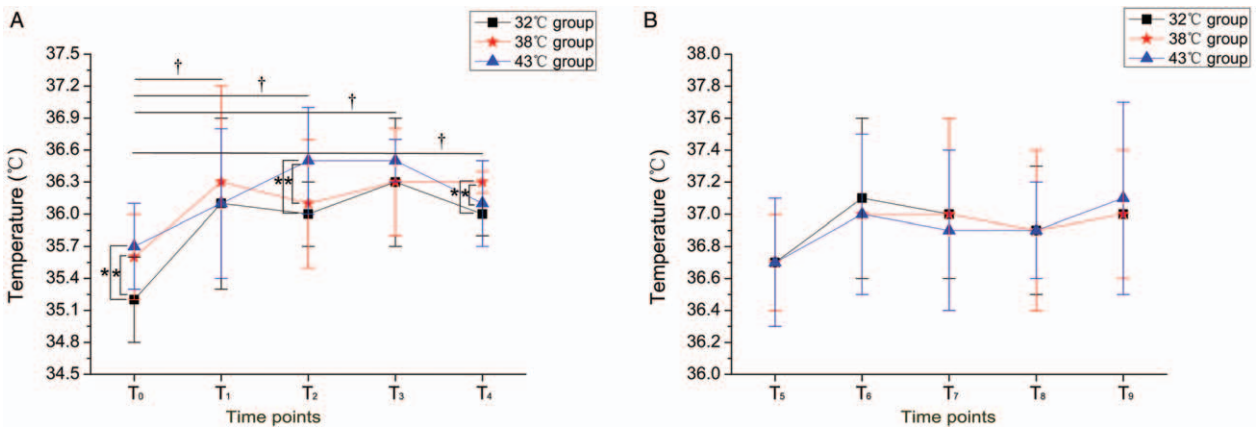

Figure 1: Time course of body temperature changes in the 32, 38, and 43°C groups. Body temperature during the operation intubation [T_0], at initial incision [T_1], at 1 h after incision [T_2], at 2 h after incision [T_3], at the end of surgery [T_4] (A) and after the operation immediately upon return to the ward after surgery [T_5], and then at 12 h [T_6], 24 h [T_7], 36 h [T_8], and 48 h [T_9] after the surgery (B) in the 32, 38, and 43°C groups. $^{*}P < 0.05$ between groups at the same time point; $^{\dagger}P < 0.05$ between groups at different time points.

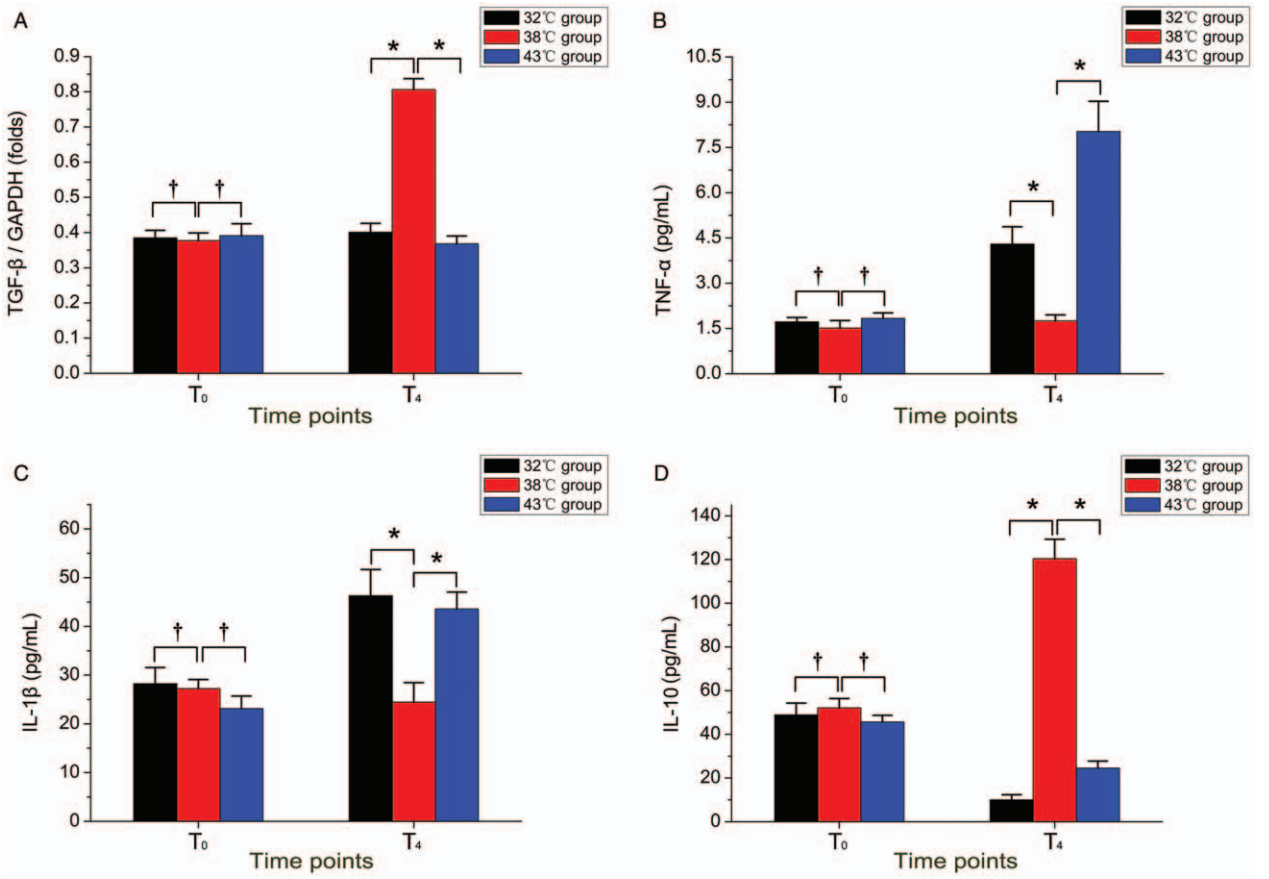

Figure 2: Serum levels of TGF-β (A), TNF-α (B), IL-1β (C), and IL-10 (D) at T_0 and T_4 in the 32, 38, and 43°C groups. Venous blood was taken at T_0 and T_4. $^{*}P < 0.05$ between groups at the same time point; $^{\dagger}P > 0.05$ between groups at the same time point. TGF: Transforming growth factors; TNF-α: Tumor necrosis factor-α; IL: Interleukin.

temperature in the 43°C group may be due to increased perspiration and that over-inhalation of warmed air triggers a negative feedback regulation after the rapid increase in body temperature seen at T_2 to T_3. Therefore, gradual changes in the body temperature, even in children with hypothermia, are appropriate, and the forced-air warming blanket should be set at the temperature of 38°C to maintain a stable body temperature.

Good control of intra-operative body temperature can promote post-operative rehabilitation.[17] Qin *et al*[18] reported that hypothermia due to poor thermal control aggravates the early inflammatory reaction after surgical trauma and is associated with poor prognosis. In this study, we found that although the body temperature can be maintained in the normal range by the use of forced-air warming blankets at temperatures of 32, 38, and 43°C, the temperature of 38°C rapidly corrected hypothermia during anesthesia induction and maintained more stable body temperature. In addition, at T_4, the serum levels of TGF-β and IL-10 were significantly higher and the serum levels of TNF-α and IL-1β were significantly lower in the 38°C group compared with levels in the 32 and 43°C groups. TGF-β and IL-10 are anti-inflammatory cytokines that inhibit immune function and suppress inflammation,[9,19] whereas TNF-α and IL-1β are pro-inflammatory cytokines that induce inflammation.[20] Our findings suggest that a forced-air warming blanket set at the temperature of 38°C may produce an anti-inflammatory effect, which may explain the reduced incidence of post-operative fever in the 38°C group.

Changes in the serum level of inflammatory cytokines are sensitive indicators of the stress response in children[21] and are affected by various factors including pain, blood loss, hypothermia, and operative duration.[22] It has been shown that activation of the TGF-β signaling pathway is regulated by temperature.[23,24] Consistent with these findings, we found that that the serum level of TGF-β was higher in the 38°C group than in the 32 and 43°C groups. This may be because 38°C, the temperature closest to a child's physiologic temperature, resulted in balanced metabolism, which promoted the activation of TGF-β. In summary, we found that use of a forced-air warming blanket set at the temperature of 38°C maintained a stable body temperature with a reduced incidence of post-operative fever in pediatric patients undergoing surgery for DDH. The serum levels of the anti-inflammatory cytokines TGF-β and IL-10 were increased and those of the pro-inflammatory cytokines TNF-α and IL-1β were decreased in patients treated with a forced-air warming blanket set at the temperature of 38°C. Our findings suggest that a forced-air warming blanket set at the temperature of 38°C should be used to prevent hypothermia in pediatric patients undergoing surgery for DDH.

In conclusions, force-air warming blankets set at 38°C maintained stable body temperature with less adverse outcome and effectively inhibited the inflammatory response in pediatric patients undergoing surgery for DDH.

Funding

This work was supported by grants from the Guangzhou Institute of Pediatrics/Guangzhou Women and Children's Medical Center (No. YIP-2018-037 and YIP-2019-061).

Conflicts of interest

None.

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How to cite this article: He LP, Liu PZ, Wen YM, Wu J. Effect of temperature maintenance by forced-air warming blankets of different temperatures on changes in inflammatory factors in children undergoing congenital hip dislocation surgery. Chin Med J 2020;133:1768–1773. doi: 10.1097/CM9.0000000000000846