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The relationship between intraoperative body temperature and thiol/disulfide balance in geriatric patients undergoing elective transurethral prostate resection surgery with spinal anesthesia

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Abstract. – OBJECTIVE: We aimed to investigate the relationship between intraoperative body temperature and thiol/disulfide balance in geriatric patients scheduled for elective transurethral prostate resection surgery with spinal anesthesia.

PATIENTS AND METHODS: 71 patients classified as categories 1 and 2, according to American Society of Anesthesiologists (ASA) classification, were included in the study. The core temperature of the patients was recorded in the operating room after monitoring, at 5 and 30 minutes after spinal anesthesia. Total thiols, native thiols, disulfide amounts, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol were calculated as percentages after monitorization ($T_{preoperative}$) and at 60 minutes after spinal anesthesia ($T_{intraoperative}$).

RESULTS: The disulfide levels in the $T_{intraoperative}$ period (29±8.9 mmol/L) were higher than the disulfide levels measured in the $T_{preoperative}$ period (18.2±8.8 mmol/L) (p<0.001). In the $T_{preoperative}$ period, the disulfide/native thiol (%) level was 4.6±2, while the disulfide/total thiol (%) level was 4.2±1.6. In the $T_{intraoperative}$ period, the disulfide/native thiol (%) level was 8±2.3, while the disulfide/total thiol (%) level was 6.8±1.7. Native thiol/total thiol (%) levels for the $T_{preoperative}$ and $T_{intraoperative}$ periods were 91.5±3.3 mmol/L and 86.3±3.4 mmol/L, respectively. A correlation was found between native, total thiol levels and patient age in the $T_{preoperative}$ and $T_{intraoperative}$ periods.

CONCLUSIONS: Oxidative stress can be reduced in geriatric patients with the possibility of developing involuntary perioperative hypothermia by regularly monitoring body temperature and applying warming techniques.

Key Words:
Thiols, Disulfides, Transurethral prostate resection, Hypothermia, Oxidative stress.

Introduction

Transurethral resection of the prostate (TURP), which is performed to eliminate obstruction caused by benign prostatic hyperplasia, is an effective method to improve the quality of life of patients[1,2]. However, in addition to complications such as bleeding, extravasation of irrigation fluid, perforation of the prostate capsule, transurethral resection syndrome, and bladder neck perforation during the procedure[3,4], involuntary perioperative hypothermia (IPH) may develop during the intraoperative period, depending on the temperature and amount of irrigation fluid used during the procedure[5].

IPH is defined[6] as a drop to below 36°C in body temperature between the preoperative period and the postoperative period. Cellular level effects and clinical complications, such as a decrease in subcutaneous oxygen pressure[7], T cell-mediated antibody production, and neutrophil functions[8], as well as myocardial ischemia[9] and an increase in surgical site infections[10,11], have been reported[7-11] as a result of IPH.

There are sufficient antioxidant defense mechanisms to cope with reactive oxygen species

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under normal physiological conditions. However, oxidative stress (OS) may occur when this balance is disturbed by various effects related to a patient's metabolic state, surgery, or anesthesia. We thought that IPH could also cause OS due to the effects listed above.

According to the current literature[12,13], OS markers such as malondialdehyde and total antioxidant capacity have been used to detect OS. Dynamic thiol/disulfide balance, developed by Erel and Neselioglu[14], can also be used as an OS marker.

Thiol-disulfide homeostasis is the reversal of thiol oxidation and represents the levels of disulfides and thiols. Thiol-disulfide homeostasis is an important indicator, which shows several biochemical properties related to OS; it has been associated[15,16] with various diseases, including cardiac pathologies, endocrine disorders, neurologic diseases, pulmonary diseases, gastrointestinal disorders, and psychiatric disorders, as well as several surgical operations.

We planned a prospective observational study to examine the effects of IPH on OS. We aimed to investigate the relationship between intraoperative body temperature and thiol/disulfide balance in patients scheduled for elective TURP surgery with spinal anesthesia.

Patients and Methods

After obtaining approval from the Ethics Committee of Recep Tayyip Erdogan University (date: 27/04/2018, number decision: 2018/87), adult patients who were scheduled for elective TURP surgery due to benign prostatic hyperplasia and who signed the written informed consent form were included in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The following patients were excluded from the study: patients whose physical score was 3 or higher according to the American Society of Anesthesiologists (ASA); patients who could not undergo spinal anesthesia due to patient preference or medical reasons; patients whose body temperature taken one hour before the surgery was outside the range of 36-37.5°C; patients who needed additional oxygen during the perioperative period; patients with a medical history of thyroid disease, malignant hyperthermia, or thermoregulation abnormalities, including neuroleptic malignant syndrome; patients with a medical history of ear infection, uncontrolled hypertension, neurological disease, psychiatric disease, vertebral column deformity, coagulation disorder, alcohol and/or drug addiction, and drug allergy. All operations were performed by the same surgical team.

Spinal Anesthesia and Monitoring

A standardized follow-up procedure was applied to all patients. The operating room temperature was maintained in the range of 22-24°C. The left brachial vein was cannulated with an 18-gauge cannula for intravenous (iv) hydration and drug administration thirty minutes before the operation. A 20-gauge iv cannula was placed on the dorsum of the right hand to collect venous blood samples for research purposes. Three-channel electrocardiogram, non-invasive arterial blood pressure, and peripheral oxygen saturation (SpO_2) monitoring were applied in the operating room to patients who were not given premedication. After being taken to the operating room, patients were given an 8-mL/kg iv bolus and a 2-mL/kg/hr continuous 0.9% NaCl iv infusion. All iv fluids used during surgery were kept at operating room temperature.

Spinal anesthesia was applied at the L_{3-4} or L_{4-5} level in the lateral decubitus position using a 25-gauge spinal needle. With the pinprick test, sensory block at the T8 dermatome level was accepted as adequate anesthesia.

Prophylactic oxygen was not administered to the patients. Hypotension was defined as > 30% drop in baseline systolic blood pressure and was treated with doses of 5 mg iv ephedrine at 1-minute intervals until the systolic blood pressure became > 100 mmHg. Patients who developed hypotension were administered 3 ml/Kg iv 0.9% NaCl solution as a bolus, as needed. A decrease in the heart apex rate below 45 bpm was defined as bradycardia and was treated with 0.01 mg/Kg iv atropine bolus infusions until the heart apex rate became > 45 bpm.

Warm saline solution was used as a surgical irrigation fluid in all operations. All patients were covered with a double-warmed cotton blanket from the neck to the umbilicus to protect against heat loss.

TUR-P Surgical Procedure

The prostate tissue causing the obstruction was resected gradually from the bladder neck by the Mauermayer method, based on the principle of starting at 6 o'clock and forming the verumontanum as its distal border. The resectoscope shaft of Olympus with bipolar energy was used at 200-watt cutting and 100-watt coagulation energy. An isotonic saline solution (0.9% NaCl) was used as irrigation fluid during the procedure.

Measurements and Records

Patient characteristics, including age, height, weight, body mass index (BMI), and ASA physical score, as well as surgical data, including operation time, amount of bleeding, and amount of irrigation fluid used, were recorded. After-monitoring, including mean arterial blood pressure (MAP), heart rate (HR), and SpO_2 values were recorded at 5, 10, and 15 minutes following spinal anesthesia and, thereafter, at 10-minute intervals. The core temperature of patients was measured and recorded using an infrared tympanic thermometer (ThermoScan IRT 6020, Braun, Germany). The same ear was used for all measurements. The preoperative body temperature of the patients was measured twice at intervals of 5 and 10 seconds from the tympanic membrane with a digital thermometer of the same brand, and the lowest value was recorded. The core temperature of the patients was recorded in the operating room five minutes after spinal anesthesia and at 30-minute intervals thereafter.

Thiol/Disulfide Studies

Venous blood samples were taken in biochemistry tubes containing coded anticoagulant and serum separator after monitoring in the operation room (Tpreoperative) and 60 minutes (Tintraoperative) after spinal anesthesia. The tubes were centrifuged at 1,500 rpm for 10 minutes and stored frozen at -80°C in a dry environment. With the automatic spectrophotometric method developed by Erel and Neselioglu[14], half of the difference between total thiols and native thiols was determined as the dynamic disulfide amount. After studying total thiols and native thiols, disulfide amounts (i.e., disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol) were calculated as percentages.

Statistical Analysis

Sample size and power were calculated with G*Power (Franz Foul, Universität Kiel, Kiel, Germany) v.3.1.9.4. The sample size was determined as 51 by taking an effect size of 0.4, a value of 0.05, a value of 0.2, and a confidence interval of 0.95. Considering measurement deficiencies, 80 patients were planned to be included in the study.

Data were analyzed using SPSS (IBM Corp., Armonk, NY, USA). Patient characteristics were analyzed using descriptive statistics. The distribution of data was evaluated using the Kolmogorov-Smirnov test. Native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol percentage ratios are shown as mean±standard deviation due to normal distribution; preoperative and intraoperative data were compared using dependent samples *t*-tests.

Operating room temperature, intraoperative body temperature, HR, MAP, SpO_2, iv hydration fluid amount, irrigation fluid amount, and disulfide/native thiol percentage ratios are shown as medians (interquartile width), since they did not comply with normal distribution; preoperative and intraoperative data were compared with the Wilcoxon-signed rank test. Categorical data were shown as numbers (%). Comparisons were made with the Chi-square test. Relationships between age, irrigation fluid, and thiol/disulfide parameters were analyzed using Pearson's correlation coefficient test. Relationships between BMI, which did not conform to normal distribution, and thiol/disulfide parameters were analyzed using the Spearman correlation coefficient test. Statistical significance was accepted as $p<0.05$ in all analyses.

Results

A total of 76 patients were included in the study. Five patients were excluded due to hemolysis of their blood samples; thus, the data of 71 patients were evaluated. The mean operational time was measured as 84±21 minutes, and the mean length of stay in the hospital was 2.5±0.5 days. The mean age of the patients was 67.7±2.5 years. Mean body temperature was calculated as 36.5±0.2°C and 35.5±0.2°C for the preoperative and intraoperative periods, respectively ($p<0.001$). Patient characteristics and data for the preoperative period are provided in Table I. The disulfide levels in the $T_{intraoperative}$ period (29±8.9 mmol/L) were higher than the disulfide levels measured in the $T_{preoperative}$ period (18.2±8.8 mmol/L; $p<0.001$) (Figure 1). In the $T_{preoperative}$ period, the disulfide/native thiol (%) level was 4.6±2, while the disulfide/total thiol (%) level was 4.2±1.6. In the $T_{intraoperative}$ period, the disulfide/native thiol (%) level was 8±2.3, while the

Table I. Patient characteristics and surgical measurements.

Parameter	Mean	± SD
Age, year	67.7	2.5
BMI, kg/m²	28.1	4.5
	n	**%**
ASA physical score II	31	44
Operation duration (min)	84	21
Length of stay (days)	2.5	0.5
Intraoperative iv fluid amount (mL)	1,247.1	395.4
Irrigation fluid amount (L)	23.4	8.6
Body temperature (°C)		
$T_{preoperative}$	36.5	0.2
$T_{intraoperative}$	35.5	0.2
Operating room temperature (°C)		
$T_{preoperative}$	22.1	0.7
$T_{intraoperative}$	22.1	0.7

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; iv: intravenous; $T_{preoperative}$: after monitoring in the operating room; $T_{intraoperative}$: 60 minutes after spinal anesthesia; SD: Standard Deviation.

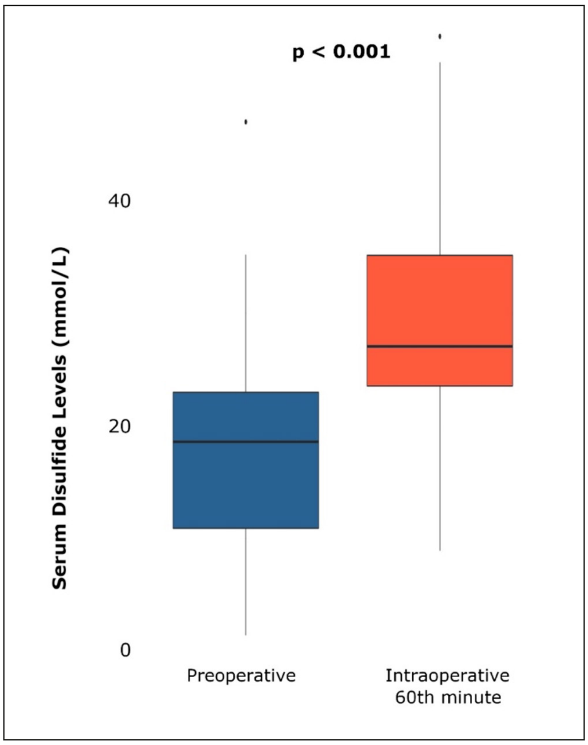

Figure 1. Serum disulfide levels.

disulfide/total thiol (%) level was 6.8±1.7. Disulfide/native thiol (%) and disulfide/total thiol (%) levels increased significantly in the $T_{intraoperative}$ period compared to the $T_{preoperative}$ period (*p*<0.001) (Figure 2).

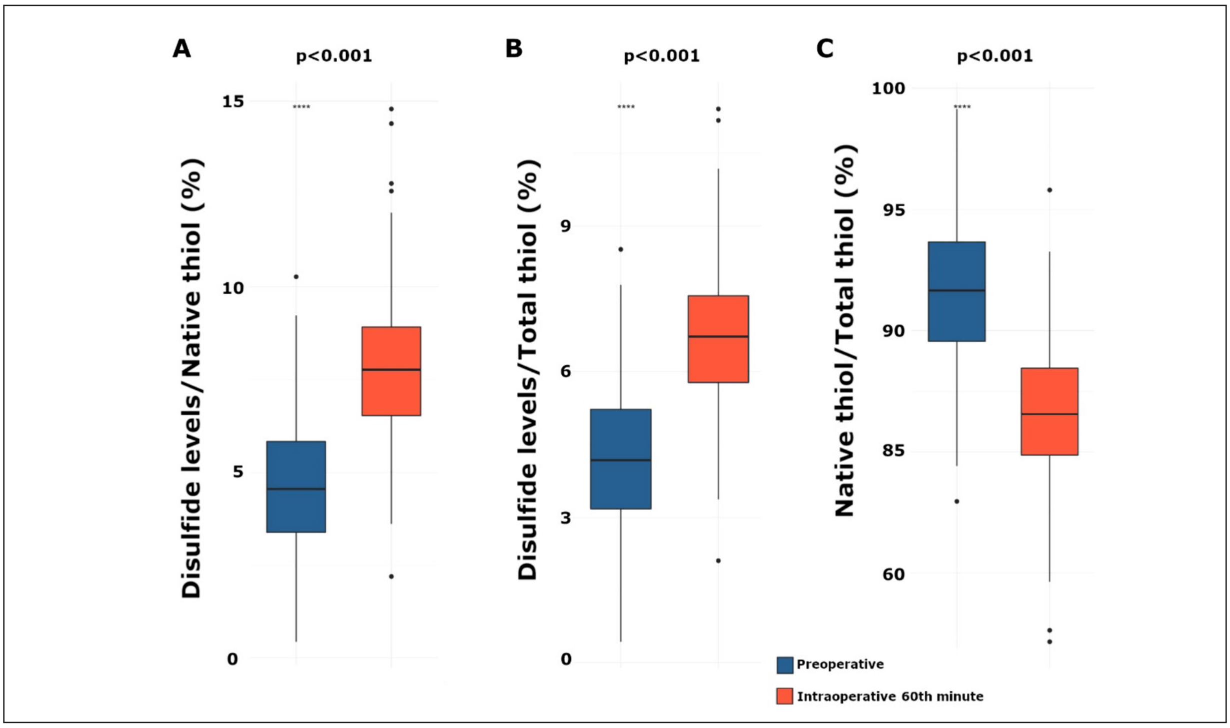

Figure 2. Disulfide/native thiol, disulfide/total thiol, native thiol/total thiol rates (%). **A**, Disulfide levels/native thiol (%). **B**, Disulfide/total thiol (%). **C**, Native thiol/total thiol (%).

Native thiol/total thiol (%) levels for the $T_{preoperative}$ and $T_{intraoperative}$ periods were 91.5±3.3 mmol/L and 86.3±3.4 mmol/L, respectively. In addition, native thiol/total thiol (%) levels in the $T_{preoperative}$ period were higher compared to the $T_{intraoperative}$ period ($p<0.001$) (Figure 2). In the comparison of native thiol and total thiol parameters during the $T_{preoperative}$ and $T_{intraoperative}$ periods, no statistically significant difference was found ($p>0.05$) (Table II). A correlation was found between native thiol, total thiol levels, and patient age in the $T_{preoperative}$ and $T_{intraoperative}$ periods (r = -0.484, p=0.000; r = -0.466, p=0.000; r= -0.273, p=0.021; r= -0.253, p=0.03, respectively). No correlation between BMI and the total amount of irrigation fluid used intraoperatively and thiol parameters ($p>0.05$) was detected.

Discussion

Perioperative inadvertent hypothermia has a high incidence in patients undergoing TURP or transurethral resection of the prostate[17]. On the other hand, room temperature and warmed irrigation water have been demonstrated[18,19] to increase core body temperature. Therefore, warmed irrigation water can be used to decrease the magnitude of inadvertent hypothermia during TURP. Several studies[20,21] have reported several techniques to warm the patient other than the use of warmed irrigating water, including forced air warming system, and electric blanket. Some authors[21] advocate that warmed irrigation water should be used in conjunction with patient warming devices.

In the present prospective observational study, it was found that in elective TURP operations performed with spinal anesthesia, despite the maintenance of room temperature and the use of warm irrigation fluids, the body temperature of the patients decreased by 1°C, and the thiol/disulfide balance was disrupted in favor of disulfide. The effect of IPH on OS is an issue that has not been fully clarified in the literature. The pathophysiology of OS is closely linked to inflammation, mitochondrial dysfunction, and ischemia/reperfusion injury in the case of surgery[22]. Perioperative OS is a complex response that depends on individual patient-related differences, comorbidities, the extent of tissue damage due to surgery, and anesthetic factors (duration of anesthesia, method). Age is also among the factors affecting perioperative OS[23,24]. Considering all these factors, we found that native thiol and total thiol levels, which are indicators of OS in our geriatric patients, decreased with increasing age in the hypothermic period. Therefore, we assume that age may be a parameter in the emergence of OS in our patients in the hypothermic period.

Studies in literature have shown different results related to the effect of hypothermia on oxidative stress markers. Wenisch et al[25] reported that mild perioperative hypothermia (a core temperature 1-3°C below normal) significantly reduced neutrophil oxidative and phagocytic capacities intraoperatively, and this could lead to a decrease in infection resistance due to hypothermia. In another study by Bailin et al[26] involving 60 patients who underwent abdominal surgery, normothermic and hypothermic groups were compared in terms of immune response. It was found that a decrease of 1°C below normal core temperature suppressed mitogen-induced activation of lymphocytes, decreased certain cytokines (IL-1β, IL-2), and caused changes in immunity in the perioperative period. Oliveira et al[27] reported that perioperative hypothermia

Table I. Thiol/disulfide balance parameters.

Parameter	$T_{preoperative}$ Mean	$T_{preoperative}$ ± SD	$T_{intraoperative}$ Mean	$T_{intraoperative}$ ± SD	*p*-value
Native thiol (mmol/L)	385.2	87.1	374	86.5	0.102
Total thiol (mmol/L)	421.8	97.6	432.2	96.3	0.217
Disulfide (mmol/L)	18.2	8.8	29	8.9	**< 0.001**
Disulfide/native thiol (%)	4.6	2	8	2.3	**< 0.001**
Disulfide/total thiol (%)	4.2	1.6	6.8	1.7	**< 0.001**
Native thiol/total thiol (%)	91.5	3.3	86.3	3.4	**< 0.001**

$T_{preoperative}$: After monitoringin the operating room; $T_{intraoperative}$: 60 minutes after spinal anesthesia; SD: Standard Deviation.

in rats decreased superoxide dismutase, catalase, and glutathione, while colonic anastomoses increased lipid peroxidation in scar tissue.

In an animal study[28] conducted differently from the studies mentioned above, it was determined that the effects of moderate hypothermia weakened systemic OS was associated with experimental intestinal ischemia/reperfusion injury and, as a result, lipid peroxidation was reduced in the lungs and kidneys with plasma. The authors concluded that the reduction of systemic nitric oxide production and the prevention of intestinal glutathione depletion were effective in this result. Drapalova et al[29] predicted that deep hypothermia in patients undergoing elective cardiac surgery suppressed the development of systemic inflammatory response and delayed the onset of local adipose tissue inflammation, thus providing protection against excessive presentation of proinflammatory and hypoxia-related factors.

In the literature, we did not find any studies investigating the effect of IPH on thiol/disulfide balance. The dynamic thiol/disulfide balance in the body depends on free oxygen radical production and thiol reserves[30]. Thiols form a less toxic byproduct by forming disulfide bonds with free oxygen radicals produced in the body[31]. Therefore, a high number of disulfide bonds indicates an increase in the production of free oxygen radicals. Studies[32,33] have shown that OS decreases native thiol levels while increasing disulfide bond formation. In our study, in the period in which our patients were hypothermic, disulfide levels were found to be higher compared to the normothermic period, while native/total thiol (%) levels were lower. We interpreted this to indicate that hypothermia might have triggered OS through thiol/disulfide parameters, as previously shown by other oxidative stress markers.

Limitations

Although the study achieved important results, it still has the following limitations. First, the relationship with IPH can be determined by evaluating the size and weight of the prostate and following the surgical bleeding degree or score. Second, applying continuous fluid warming devices and other external measures to reduce temperature loss may provide patient benefits. Third, when the irrigation fluid is heated to 17°C-36°C, its density and viscosity may change. It can increase the average absorption of irrigation fluid by around 54%. Therefore, it can lead to a 65% shortening of the safe time for surgery[34]. Fourth, a blood sample could be drawn 24 hours after surgery to examine the thiol/disulfide balance and provide more detailed information on its elimination. In addition, the concentration of stress response hormones could be studied. They could help us better understand the changes in stress levels with hypothermia.

Conclusions

The use of room temperature or unheated irrigation fluids during TURP may reduce body temperature. It should be considered that these factors may contribute to intraoperative hypothermia in geriatric patients. In this study, body temperature during TURP decreased by 1°C compared to the preoperative baseline value. In addition, the disulfide component of oxidative stress increased in patients compared to the intraoperative baseline value. Based on this relationship, oxidative stress can be reduced by regular monitoring of body temperature and applying warming techniques in geriatric patients who are likely to develop involuntary hypothermia. Simple and inexpensive warming methods can be applied in geriatric patients undergoing TURP. With these methods, organ functions can be preserved by keeping body temperature within normal limits.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

Ethics approval was received from the Ethics Committee of Recep Tayyip Erdogan University (date: 27/04/2018, number decision: 2018/87).

Informed Consent

Patients were informed in detail about the objectives of the study and gave written consent.

Authors' Contribution

LK: Conception and design, interpretation, final approval. SB: Acquisition of data, analysis, interpretation. MA: Acquisition of data, analysis, and interpretation. HB: Interpretation and final approval. OE: Supervision, final approval.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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