Acute normovolemic hemodilution reduced allogeneic blood transfusion without increasing perioperative complications in patients undergoing free-flap reconstruction of the head and neck

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Abstract
Purpose The present case–control study was conducted to evaluate whether acute normovolemic hemodilution (ANH) can reduce the need for perioperative allogeneic blood transfusion (ABT) and affect the incidence of perioperative complications in free-flap reconstruction of the head and neck.

Methods This single-center, retrospective, observational study included the perioperative data of 123 patients who underwent free-flap reconstruction of the head and neck following oncological surgery. Patients were divided into the following two groups according to whether they received ANH: ANH group and non-ANH group. We investigated whether ANH can reduce the need for perioperative ABT using propensity score-adjusted logistic regression analysis.

Results Of the 123 patients, 113 patients were assessed; 57 patients were in the ANH group and 56 patients were in the non-ANH group. The rate [ANH group vs. non-ANH group, \( n \) (%): 2 (3.5%) vs. 23 (41.1%), \( p < 0.0001 \)] and amount [median (IQR): 0 mL (0, 0) vs. 0 mL (0, 280), \( p < 0.0001 \)] of ABT were significantly lower in the ANH group than in the non-ANH group. Propensity score-adjusted multivariate logistic regression analysis indicated that ANH use [odds ratio (OR): 0.040; 95% confidence interval (CI) 0.005, 0.320; \( p = 0.0024 \)] was one of the independent predictors of perioperative ABT. There were no significant differences in the incidences of post-operative complications between the two groups.

Conclusion ANH use can reduce the need for perioperative ABT in patients undergoing free-flap reconstruction of the head and neck without increasing the incidence of post-operative complications.

Keywords Acute normovolemic hemodilution · Free-flap reconstruction of the head and neck · Allogeneic blood transfusion · Post-operative complication · Oncological surgery

Introduction
Perioperative allogeneic blood transfusion (ABT) is often required (12–84%) in patients undergoing free-flap reconstruction of the head and neck following oncological surgery [1] because of the adoption of complicated procedures, including tumor resection, tracheostomy, free-flap harvesting, and microvascular anastomosis, which are associated with significant blood loss.

Perioperative ABT can increase the risk of various complications, such as transfusion-related acute lung injury, circulatory overload, and anaphylactic reactions [2]. Perioperative ABT has been demonstrated to be associated with poor outcomes because of ABT-induced systemic inflammation and immune suppression [3]. Particularly, immune suppression has been reported to cause cancer recurrence and metastasis in patients undergoing oncological surgery [4, 5]. A retrospective cohort study demonstrated that ABT in patients undergoing head-and-neck free-flap surgery caused prolongation of hospital stay after surgery and caused flap-related (hematoma and wound dehiscence), cardiac (myocardial infarction and congestive heart failure), and respiratory complications (respiratory distress and pneumonia) [6].
Thus, strategies to prevent or reduce ABT are required to improve the prognosis of cancer patients.

Acute normovolemic hemodilution (ANH) is one of the strategies to reduce the need for perioperative ABT, and it is currently being used worldwide, particularly in cardiac surgery [7]. A systematic review and meta-analysis reported that ANH has the potential to reduce the rate and amount of ABT because of less erythrocyte loss after hemodilution [8]. However, there has been no clinical investigation on the efficacy of ANH for reducing the need for perioperative ABT in free-flap reconstruction of the head and neck. Moreover, ANH reduces hematocrit during the surgical procedure and that contribute to the reduction in erythrocyte mass loss; however, hemodilution and fluid management could change the oxygen supply to the flap and post-operative course. The safety of ANH in reconstruction of the head and neck are still controversial. If ANH can reduce the rate and amount of ABT in free-flap reconstruction of the head and neck without increasing the incidence of post-operative complications, it could be an option which improves outcomes including cancer recurrence, post-operative infection, and flap success rate.

The present case–control study was performed to determine whether ANH can reduce the need for perioperative ABT and to evaluate whether ANH affects the incidence of perioperative complications in free-flap reconstruction of the head and neck following oncological surgery.

Methods

Study procedure and patients

This single-center, retrospective, observational study was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine, Hirosaki, Japan and was publicized on our department homepage (2019–1013). The requirement of written informed consent from the patients was waived because of the retrospective nature of the study, and the Ethics Committee approved the waiver. This study enrolled 123 patients who underwent free-flap reconstruction of the head and neck following oncological surgery at Hirosaki University Hospital between April 1, 2013 and March 31, 2019. Patients were excluded if they had pre-operative anemia (hemoglobin [Hb] level less than 10.0 g/dL), severe liver disease (Child–Pugh grade B or C), severe heart failure (New York Heart Association functional class 3 or 4), and end-stage kidney disease requiring intermittent hemodialysis, because these conditions met exclusion criteria for ANH. As low-volume ANH (5–8 mL/kg) has been reported to be ineffective for reducing the need for allogeneic transfusion and post-operative bleeding [9], patients with an ANH withdrawal volume of less than 600 mL were excluded from the analysis. Patient characteristics and perioperative data were obtained from our hospital electronic medical and anesthesia records. Patient characteristics included sex, age, body mass index (BMI), medical history, American Society of Anesthesiologists Physical Status (ASA-PS), diagnosis, pre-operative anticancer therapy, and TNM classification of malignant tumors. Perioperative data included ANH use, flap type (osseous or non-osseous), surgery duration, intraoperative crystalloid and colloid fluid administration, intraoperative blood loss and urine output, ABT amount until discharge from the intensive-care unit (ICU), ICU stay duration, and mechanical ventilation duration. The following pre- and post-operative laboratory data were measured when patients were admitted to the ICU: Hb level, hematocrit, platelet count, blood urea nitrogen level, creatinine level, lactate level, prothrombin time, activated partial thromboplastin time, fibrinogen level, and post-operative inotropic use. Additionally, Hb level, hematocrit and lactate level after hemodilution, intraoperative nadir Hb level and hematocrit, and maximum lactate level were assessed. Post-operative complications included flap failure with impaired blood flow, post-operative bleeding requiring hemostasis, surgical site infection, acute kidney injury, atrial fibrillation, and acute heart failure. Flap failure with impaired blood flow was classified into three categories: salvaged flap failure (flap ischemia salvaged by re-microvascular surgery), partial necrosis needed debridement, and total necrosis needed re-reconstruction. Additionally, we assessed death 0–90 days and 0–180 days after surgery. Patients were divided into the following two groups according to ANH use: ANH group and non-ANH group.

Anesthesia and ANH procedure

The principle indication for ANH in our institution is an estimated blood loss of more than 500 mL or a request from a surgeon for a patient with an Hb level of more than 10 g/dL. Exclusion criteria for ANH in our institution were uncontrolled congenital heart failure (New York Heart Association functional class 3 or 4) including active ischemic heart disease, severe liver disease (Child–Pugh grade B or C), and refusal by the patient, in addition to pre-operative anemia (Hb level less than 10 g/dL) and renal failure which were considered to be absolute contraindication for ANH [10]. The reason why patients with congenital heart failure including active ischemic heart disease and severe liver disease (Child–Pugh grade B or C) are excluded is that hemodilution can worsen these conditions because of reducing oxygen supply.

All surgeries were performed under general anesthesia and standard monitoring with FloTrac/Vigileo system (Edwards Lifescience, Tokyo, Japan). Even though our institution does not have specific protocol for fluid management,
we carefully control fluid volume by referring to stroke volume variation. We usually maintain stroke volume variation between 10 and 14% after hemodilution considering reinfusion of collected blood and adjust stroke volume variation < 10% after reinfusion of collected blood. General anesthesia was induced and maintained with propofol, ketamine, remifentanil, and/or fentanyl and rocuronium. After anesthetic induction, blood was withdrawn from the central venous line, and the withdrawn blood volume for ANH was selected to avoid an Hb level of less than 8.0 g/dL after hemodilution. The withdrawn blood volume was simultaneously replaced with an equal volume of 6% hydroxyethyl starch solution (130/4) (Volven; Fresenius Kabi, Bad Homburg, Germany). The collected blood was stored in a standard blood collection pack (JMS Blood Bag CPD400; JMS, Tokyo, Japan) at room temperature (22–26 °C) on a shaker. Arterial blood gas analysis was performed and Hb and lactate levels were measured immediately after hemodilution and at least every 2 h during surgery to evaluate oxygen delivery to peripheral tissues. When microvascular anastomosis was completed, the collected blood was reinfused to the patients.

**Criteria for ABT**

In our institution, the transfusion threshold is generally set at an Hb level of less than 7.0 g/dL. Additionally, for cases involving an increased risk of ischemia, such as cases of pulmonary disease, coronary artery disease, and cerebral vascular disease, and cases showing new electrocardiographic signs of cardiac ischemia, the transfusion threshold is set at an Hb level of less than 9.0 g/dL.

**Statistical analysis**

Patient characteristics and perioperative data are presented as median (25th–75th percentile) and number (percentage of each group). All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Statistical differences between the study groups were assessed using Fisher’s exact test for categorical variables and Student’s t test or the Mann–Whitney U test for continuous variables.

Propensity score-adjusted multivariate logistic regression analysis [11] was performed to evaluate whether ANH use can reduce the need for ABT. The propensity score was the predicted probability of being in the ANH group considering the covariate values in multivariate logistic regression analysis. The selected covariates included not only age, sex, BMI, ASA-PS of ≥3, pre-operative Hb level, and pre-operative anticancer therapy but also T3 stage or T4 stage and osseous free-flap reconstruction according to the existing knowledge that these were predictors of perioperative ABT [1]. We used the propensity score as a covariate in our model to adjust for pre-operative confounding factors. The presence of ANH was forced into the model as an explanatory variable. In addition, as intraoperative blood loss is related with perioperative ABT, this variable was forced into the model as a predictor. It has been suggested that the number of events per predictor variable in multivariate logistic regression analysis should be at least 10 to provide an adequate predictive model [12]. However, a recent simulation study suggested that 5–9 events per predictor variable were sufficient [13]. In this study, considering the number of events (25 patients received ABT), three variables were included in the model (one variable was included in the model for eight events). Variance inflation factor (VIF) was used to check for multicollinearity among the variables. Discrimination was measured using the area under the curve (AUC). The results are expressed as adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

All data analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) and EZR software version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A p value of < 0.05 was considered statistically significant in all tests.

**Results**

Of the 123 enrolled patients, 113 were finally statistically analyzed (Fig. 1). All patients were estimated more than 500 mL of blood loss. Their characteristics are presented in Table 1. Of the 113 patients, 57 were included in the ANH group and 56 were included in the non-ANH group. There were no significant differences in sex, BMI, ASA-PS, medical history, pre-operative anticancer therapy, cancer stage, cancer type, and flap between the groups. However, age was significantly different between the groups.

The perioperative data are presented in Table 2. In the ANH group, the ANH volume was 600 mL in three patients, 800 mL in 51 patients, and 1200 mL in three patients, and Hb level after hemodilution was 9.1 g/dL (8.4, 9.9). Among all study patients, 25 (22.1%) received perioperative ABT. The rate of perioperative ABT was significantly higher in the non-ANH group (41.1%) than in the ANH group (3.5%) (p < 0.0001). Additionally, the amount of ABT was significantly lower in the ANH group than in the non-ANH group (p < 0.0001). The pre-operative Hb level and hematocrit were significantly higher in the ANH group than in the non-ANH group (13.8 vs. 12.0 g/dL, p < 0.0001, 40.9% vs. 36.5%, p < 0.0001, respectively). Moreover, the post-operative Hb level and hematocrit remained higher in the ANH group (9.7 vs. 8.5 g/dL, p < 0.0001, 29% vs. 26.1%, p < 0.0001, respectively). However, intraoperative blood loss was not significantly different between the groups. Although the pre-operative and post-operative lactate level were
significantly higher in the ANH group than in non-ANH group, maximum lactate level was not significantly different between the groups. Moreover, changes in lactate level (post-operative lactate level – pre-operative lactate level) were not significantly different between the groups [0.5 mmol/L (0.1, 1.0) vs. 0.4 mmol/L (0.1, 0.7), p = 0.3822]. The surgery duration was significantly longer in the ANH group than in the non-ANH group (11.6 h [10.14, 12.76] vs. 9.8 h [8.4, 11.7], p = 0.0008). Intraoperatively, crystalloid infusion was not significantly different between the groups, but colloid infusion was significantly greater in the ANH group than in the non-ANH group (1500 vs. 1000 mL, p < 0.0001). In addition, there were no significant differences in the incidences of post-operative complications between the groups (Table 3).

The propensity score-adjusted multivariate logistic regression analysis revealed that ANH use (OR: 0.040, 95% CI 0.005, 0.320; p = 0.0024) and intraoperative blood loss (per 100 mL increase, OR: 1.400, 95% CI 1.160, 1.700; p = 0.0006) were independently associated with perioperative ABT (Table 4), suggesting that ANH use can reduce the need for perioperative ABT. No VIF value was up to 10, indicating that there was no collinearity in the model. The AUC value was 0.894 (95% CI 0.829, 0.959).

**Discussion**

The present study found that ANH can reduce the need for perioperative ABT and does not increase the incidence of perioperative complications in reconstruction of the head and neck. To the best of our knowledge, this is the first study to elucidate the efficacy of ANH for reducing the need for perioperative ABT and to assess the safety of ANH in reconstruction of the head and neck.

Although some background variables, such as age and pre-operative Hb level, significantly differed between the ANH and non-ANH groups, the rate and amount of ABT were significantly lower in the ANH group than in the non-ANH group. The propensity score-adjusted multivariate logistic regression analysis indicated that ANH use and intraoperative blood loss were independent factors associated with perioperative ABT. Additionally, there were no significant differences in the incidences of post-operative complications between the two groups. Therefore, ANH can reduce the need for perioperative ABT without increasing the risk of post-operative complications.

Although no previous studies have evaluated the efficacy of ANH for reducing the need for perioperative ABT in patients undergoing free-flap reconstruction of the head and neck, the findings of some previous studies in other surgical settings support our positive findings [7, 8, 14, 15]. A previous meta-analysis of randomized trials revealed that ANH reduced both the rate and amount of ABT in cardiac surgery [8]. Additionally, a retrospective study showed that ANH was an effective approach to reduce the need for ABT in patients undergoing gynecological cancer surgery [14]. Moreover, a prospective randomized-controlled study demonstrated that ANH reduced the rate of perioperative ABT (10% vs. 36%) in hepatectomy patients [15]. The present data showed that ANH could reduce the need for ABT in free-flap reconstruction of the head and neck following oncological surgery, which involves a long duration.

One of the concerns about ANH use is post-operative complications related with increased intraoperative fluid administration [16]. A previous randomized trial revealed that ANH use significantly increased anastomotic site complications without reducing the need for ABT when compared with standard patient management [16]. The authors mentioned that these results were likely associated with greater intraoperative fluid administration in the ANH group than in the non-ANH group (8000 vs. 6000 mL). In contrast, the present study revealed that ANH use did not increase the incidence of perioperative complications. This might
be associated with restrictive fluid management to prevent fluid overload during the perioperative period. In the present study, although intraoperative colloid infusion was significantly greater in the ANH group than in the non-ANH group, intraoperative crystalloid infusion did not differ between the groups. A previous meta-analysis of randomized-controlled trials demonstrated that perioperative goal-directed hemodynamic therapy, including restricted fluid management, could reduce the incidence of post-operative complications in major surgery [17]. Therefore, careful fluid management with reduced crystalloid infusion might avoid preventable complications.

In the univariate analysis, there was no significant difference in flap failure between the ANH and non-ANH groups. It has been reported that acute isovolemic reduction of the Hb level to 5.0 g/dL in conscious healthy resting humans does not show evidence of inadequate systemic oxygen delivery, as assessed by the lack of changes in oxygen consumption and the plasma lactate level [18]. In our institution, as the blood withdrawal volume for ANH was selected to avoid an Hb level of less than 8.0 g/dL after hemodilution and arterial blood gas analysis, Hb-level assessment and lactate-level assessment were performed at least every 2 h during surgery, ANH was conducted without an increase in the incidence of post-operative complications. In the present study, Hb level after hemodilution was more than 8.0 g/dL and maximum lactate level was not significantly different between the groups. However, the ideal Hb level for tissue oxygenation of a free flap remains unclear. Indeed, the lack of oxygen carriers during excessive hemodilution might cause hypoxic damage in surgical flaps [19]. In contrast, moderate hemodilution is known to facilitate microcirculatory blood flow in ischemic flaps by decreasing vascular resistance [20]. An animal experimentation study revealed that ANH could improve oxygenation in ischemic and hypoxic flap tissues [21]. Moreover, in a previous study, there were no differences in flap-related and medical complications between transfusion triggers of hematocrit less than 21% versus hematocrit less than 27% in free-flap reconstruction of the head and neck [22]. Thus, the present level of ANH for free-flap surgery was likely not to increase flap failure.

In the present study, there was no significant difference in intraoperative blood loss between the ANH and non-ANH groups. A previous study revealed that ANH resulted in a hypocoagulable state, but the change in clotting ability was slight, and this could not affect the amount of intraoperative blood loss [23]. Indeed, there was no significant difference in post-operative bleeding requiring hemostasis in the present study. Although the withdrawn whole blood was stored in a standard blood collection pack at room temperature (22–26 °C) on a shaker for more than approximately 8 h, the post-operative platelet count and coagulation ability

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**Table 1** Patient characteristics

|                   | ANH group | Non-ANH group | p value |
|-------------------|-----------|---------------|---------|
| n                 | 57        | 56            |         |
| Male              | 40 (70.2%)| 30 (53.6%)    | 0.0828  |
| Age (year)        | 65 (55.69,5) | 72 (65, 78)  | <0.0001*|
| BMI (kg/m²)       | 22.3 (20.5, 25.2) | 21.1 (18.8, 24.4) | 0.0743  |
| ASA-PS            | 0.2642    |               |         |
| 1 or 2            | 47 (82.5%)| 41 (73.2%)    |         |
| 3                 | 10 (17.5%)| 15 (26.8%)    |         |
| Medical history   |           |               |         |
| Hypertension      | 22 (38.6%)| 31 (55.4%)    | 0.0909  |
| DM                | 7 (12.3%) | 9 (16.1%)     | 0.6001  |
| Dyslipidemia      | 9 (15.8%) | 6 (10.7%)     | 0.5808  |
| COPD              | 5 (8.8%)  | 6 (10.7%)     | 0.7616  |
| Stroke            | 4 (7.0%)  | 3 (5.4%)      | >0.9999 |
| IHD               | 1 (1.8%)  | 4 (7.1%)      | 0.2062  |
| Risk of ischemia  | 5 (8.8%)  | 5 (8.9%)      | >0.9999 |
| Pre-operative anticancer therapy |       |               |         |
| NAC               | 2 (3.5%)  | 8 (14.3%)     | 0.0529  |
| PRT               | 5 (8.8%)  | 6 (10.7%)     | 0.7616  |
| Type of cancer    |           |               | 0.1450  |
| Oral cavity       | 46 (80.7%)| 50 (89.3%)    |         |
| Oropharynx        | 3 (5.3%)  | 3 (5.4%)      |         |
| Hypopharynx       | 3 (5.3%)  | 2 (3.6%)      |         |
| Others            | 5 (8.8%)  | 1 (1.8%)      |         |
| T stage           |           |               | 0.2110  |
| I or II           | 26 (45.6%)| 33 (58.9%)    |         |
| III or IV         | 27 (47.3%)| 22 (39.3%)    |         |
| Unknown           | 4 (7.0%)  | 1 (1.8%)      |         |
| N stage           |           |               | 0.7660  |
| 0                 | 29 (50.9%)| 25 (44.6%)    |         |
| I                 | 12 (21.1%)| 12 (21.4%)    |         |
| II                | 14 (24.6%)| 18 (32.1%)    |         |
| Unknown           | 2 (3.5%)  | 1 (1.8%)      |         |
| M stage           |           |               | >0.9999 |
| 0                 | 57 (100%) | 56 (100%)     |         |
| I                 | 0 (0%)    | 0 (0%)        |         |
| Type of flap      |           |               | 0.4897  |
| Osseous           | 3 (5.3%)  | 5 (8.9%)      |         |
| Non-osseous       | 54 (94.7%)| 51 (91.1%)    |         |

Differences between the ANH and non-ANH groups were estimated using Fisher’s exact test for categorical variables and Student’s t test or the Mann–Whitney U test for continuous variables. Data are presented as number (percentage of each group) or median (25th–75th percentile).

ANH acute normovolemic hemodilution, BMI body mass index, ASA-PS American Society of Anesthesiologists Physical Status, DM diabetes mellitus, COPD chronic obstructive pulmonary disease, IHD ischemic heart disease, NAC neoadjuvant chemotherapy, PRT pre-operative radiotherapy

*Statistical significance
Table 2  Perioperative data of the patients

|                        | Group ANH            | Group non-ANH       | p value      |
|------------------------|----------------------|---------------------|--------------|
| Perioperative Labo data|                      |                     |              |
| Hb (g/dL)              |                      |                     |              |
| Pre                    | 13.8 (13.0, 14.8)    | 12.0 (10.9, 13.1)   | <0.0001*     |
| After hemodilution      | 9.1 (8.4, 9.9)       |                     |              |
| Intra. Nadir           | 8.2 (7.2, 8.9)       | 8.0 (6.8, 9.0)      | 0.5923       |
| Post                   | 9.7 (8.9, 10.7)      | 8.5 (7.8, 9.3)      | <0.0001*     |
| Hematocrit (%)         |                      |                     |              |
| Pre                    | 40.9 (38.8, 43.6)    | 36.5 (32.9, 38.6)   | <0.0001*     |
| After hemodilution      | 27.1 (25.0, 28.3)    |                     |              |
| Intra. Nadir           | 24.3 (21.7, 25.8)    | 24.1 (20.3, 26.5)   | 0.5630       |
| Post                   | 29.0 (27, 32.3)      | 26.1 (23.9, 27.9)   | <0.0001*     |
| Plt (x10^3/µ L)        |                      |                     |              |
| Pre                    | 19.6 (16.7, 25.0)    | 19.0 (14.9, 23.5)   | 0.3100       |
| Post                   | 14.5 (11.0, 16.8)    | 12.8 (9.7, 17.4)    | 0.7689       |
| BUN (mg/dL)            |                      |                     |              |
| Pre                    | 12.0 (11, 16)        | 14 (11, 16)         | 0.1436       |
| Post                   | 9 (8, 11)            | 10 (8, 13)          | 0.1420       |
| Cre (mg/dL)            |                      |                     |              |
| Pre                    | 0.71 (0.60, 0.88)    | 0.77 (0.64, 0.93)   | 0.3911       |
| Post                   | 0.74 (0.61, 0.88)    | 0.72 (0.60, 0.87)   | 0.6835       |
| Lac (mmol/L)           |                      |                     |              |
| Pre                    | 0.9 (0.7, 1.3)       | 0.8 (0.6, 1.0)      | 0.0054*      |
| After hemodilution      | 1.0 (0.7, 1.1)       |                     |              |
| Intra. Max             | 1.3 (1.0, 1.6)       | 1.2 (0.9, 1.6)      | 0.3038       |
| Post                   | 1.5 (1.0, 2.0)       | 1.1 (0.8, 1.6)      | 0.0151*      |
| PT (s)                 |                      |                     |              |
| Pre                    | 13.6 (12.6, 14.4)    | 14.0 (12.2, 14.5)   | 0.5765       |
| Post                   | 16.2 (14.9, 16.7)    | 15.9 (13.5, 17.3)   | 0.9404       |
| APTT (s)               |                      |                     |              |
| Pre                    | 29.3 (27.8, 30.7)    | 29.2 (27.3, 31.5)   | 0.9774       |
| Post                   | 35.2 (32.3, 39.3)    | 36.3 (33.1, 39.2)   | 0.3939       |
| Fib (mg/dL)            |                      |                     |              |
| Pre                    | 333 (293, 393)       | 365 (290, 465)      | 0.2150       |
| Post                   | 288 (227, 326)       | 296 (215, 354)      | 0.6708       |
| Duration of surgery (h) | 11.6 (10.1, 12.8)    | 9.8 (8.4, 11.7)     | 0.0008*      |
| Intra. Bleeding (mL)   | 390 (282, 525)       | 465 (300, 608)      | 0.2226       |
| Intra. Bleeding (mL/kg) | 6.6 (4.7, 9.4)       | 7.9 (5.5, 11.6)     | 0.0776       |
| Intra. UO (ml/kg/h)    | 2.9 (2.3, 4.0)       | 3.4 (2.0, 4.4)      | 0.5157       |
| Intra. infusion        |                      |                     |              |
| Total (mL/kg/h)        | 7.5 (6.0, 9.1)       | 7.4 (5.9, 7.88)     | 0.6606       |
| Crystalloid (mL/kg/h)  | 5.4 (4.2, 7.2)       | 6.1 (4.3, 7.7)      | 0.2760       |
| Colloid (mL)           | 1500 (1225, 2000)    | 1000 (500, 1350)    | <0.0001*     |
| Intra. and post. ABT   |                      |                     |              |
| RBC (mL)               | 0 (0, 0)             | 0 (0, 0.280)        | <0.0001*     |
| RBC (mL/kg)            | 0 (0, 0)             | 0 (0, 5.9)          | <0.0001*     |
| RBC (N)                | 2 (3.5%)             | 23 (41.1%)          | <0.0001*     |
| FFP (mL)               | 0 (0, 0)             | 0 (0, 0)            | 0.2434       |
| FFP (mL/kg)            | 0 (0, 0)             | 0 (0, 0)            | 0.2434       |
| FFP (n)                | 0 (0%)               | 2 (3.6%)            | 0.4963       |
| PC (mL)                | 0 (0, 0)             | 0 (0, 0)            | > 0.9999     |
| PC (mL/kg)             | 0 (0, 0)             | 0 (0, 0)            | > 0.9999     |
| PC (n)                 | 0 (0%)               | 0 (0%)              | > 0.9999     |
| Intra. and post. use of inotropes |     |                     |              |
| Noradrenaline (n)      | 39 (68.4%)           | 41 (73.2%)          | 0.6800       |
| Landiolol (n)          | 10 (17.5%)           | 6 (10.7%)           | 0.4194       |
| Duration of            |                      |                     |              |
were not significantly different between the two groups. A previous study reported that storage of whole blood for 24 h at room temperature resulted in a 23% decrease in the activity of Factor VIII, but caused no significant decrease in the activities of coagulation Factor V, Factor VII, Factor XI, Factor XII, fibrinogen, antithrombin, and von Willebrand factor [24]. This study concluded that storage of whole blood at ambient temperature for 24 h has a minimal effect on the coagulation activity of plasma and that this approach is an acceptable alternative to producing plasma on the day of blood collection. Thus, ANH in prolonged surgery might not increase perioperative blood loss.

In conclusion, our study showed that ANH use can reduce the need for perioperative ABT without increasing the incidence of post-operative complications in patients undergoing...
free-flap reconstruction of the head and neck following oncological surgery.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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