Does Timing of Hemodilution Influence the Stress Response and Overall Outcome?

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This study was designed to assess the stress response of acute hemodilution (AH) in patients subjected to radical cystectomy. Forty adult male patients were randomly allocated into a control group (n = 10) where homologous blood transfusion was used, a preinduction AH group (n = 20) where AH was performed before lumbar epidural block and induction of anesthesia, and into a postinduction group (n = 10) where AH was performed after induction of anesthesia. Monitored variables included hemodynamic, hematological and coagulation factors, liver function tests, and serum hormones. AH performed in awake or in anesthetized patients did not result in significant hemodynamic disruption, or result in detectable end-organ or stress-hormone changes when compared to control patient outcomes after radical cystectomy. Hemodilution can be performed by protocol for patients who are undergoing this procedure without major adverse effects.

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Although intraoperative normovolemic hemodilution has been described by many groups (1,2), anesthesia and surgery preclude proper assessment of the stress response to hemodilution. The effects of normovolemic hemodilution during lumbar epidural anesthesia on hemodynamic function and oxygenation were minimal (3). The stress response to acute hemodilution (AH) has not been determined in an awake patient. This study was designed to assess the stress response to AH through estimations of hemodynamic, hematological, biochemical, and hormonal variables. We randomly allocated patients subjected to radical cystectomy and acute hemodilution to three groups: control, acute hemodilution while awake, or acute hemodilution after induction of anesthesia, and we compared their stress responses, hemodynamics, and organ outcomes.

Methods

This study was performed in patients suffering from carcinoma of the urinary bladder who submitted to radical cystectomy. Exclusion criteria included hemoglobin levels less than 10 $g \cdot dL^{-1}$ and major cardiovascular or respiratory diseases. The technique of acute hemodilution was explained to the patient, and a written consent was secured. The protocol was approved by the responsible authorities. Acute hemodilution was performed by withdrawal of 2 units of the patient's blood by a suitable venipuncture, and simultaneous infusion of 3 L of lactated Ringer's solution which was completed in 30 min. The pulse rate, arterial blood pressure, central venous pressure, and electrocardiograph tracing were observed during the technique of hemodilution.

Patients were given 10 mg of diazepam orally on the night of surgery and 2 h before anesthesia. Lumbar epidural analgesia was achieved by administration of a mixture of 5 mL of lidocaine 2%, 10 mL of bupivacaine 0.5%, and 2 mg of morphine through an epidural catheter. Sleeping dose of thiopental was used for induction of anesthesia, and tracheal intubation was facilitated by the IV administration of succinylcholine 1 $mg \cdot kg^{-1}$. Anesthesia was maintained by $N_2O{:}O_2$ (FIO_2 = 0.33) and halothane 0.25–0.5%. Paralysis was induced by administration of *d*-tubocurarine in an initial dose of 0.3 $mg \cdot kg^{-1}$. The patient's own blood was reinfused at the time of maximum blood loss which occurred during posterior dissection of the bladder, while the control group received homologous whole blood. Perioperative crystalloid infusion consisted of 5% dextrose in water in AH patients, while the control group received isotonic saline and 5% dextrose in water in a proportion of 2:1 at a rate of 12–15

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Table 1. Demographic Data and Operative Time in Patients Subjected to Acute Hemodilution and Radical Cystectomy

Group	*n*	Age (yr)	Body weight (kg)	Height (cm)	Operative time (h)	Blood transfusion (Units, Range)
I. Control	10	48.6 (35–61)	66.1 ± 10.3	164.4 ± 7.5	5.3 ± 0.5	2–3
II. Preinduction hemodilution	20	47.3 (33–63)	67.5 ± 10.7	167.4 ± 6.6	5.9 ± 1.0	None
III. Postinduction hemodilution	10	49.3 (43–62)	70.6 ± 11.5	159.1 ± 15.1	5.5 ± 0.5	None

Values are mean ± SD and mean (range).

$mL \cdot kg^{-1} \cdot h^{-1}$. At the end of surgery, muscle tone was regained by neostigmine, 0.04 $mg \cdot kg^{-1}$, mixed with atropine, 0.02 $mg \cdot kg^{-1}$.

The monitored perioperative variables included heart rate, continuous 3-lead electrocardiograph, noninvasive arterial blood pressure, and central venous pressure through the right subclavian vein. Venous blood samples were taken to measure hemoglobin, hematocrit, serum Na^+ and K^+, coagulation variables (platelet count, prothrombin activity, and fibrinogen concentration), liver function tests (bilirubin, transaminases, alkaline phosphatase, albumin, and globulins), and serum hormones (growth hormone, prolactin, and cortisol). Hormonal assay was determined by radioimmunoassay. Venous blood samples were collected into plain tubes, and serum was separated in refrigerated centrifuge at 1800 *g* for 10 min, and stored frozen at −20°C in aliquots. Serum hormonal levels were determined using commercially available kits from Diagnostic Product Corporation, Los Angeles, CA. The kits for cortisol and prolactin were solid-phase ^{125}I-radioimmunoassay, and the kits for growth hormone were double-antibody ^{125}I-radioimmunoassay.

Forty adult male patients were randomly allocated into three groups according to the type of replacement of blood loss and the time of acute hemodilution. The control group included 10 patients who were managed in the routine manner by which homologous blood was infused to replace the operative blood loss. The preinduction hemodilution group included 20 patients who were subjected to acute hemodilution before epidural block and induction of anesthesia. The postinduction hemodilution group included 10 patients in whom acute hemodilution was performed after induction of anesthesia and before the start of surgery.

Patients were monitored clinically and biochemically during the postoperative period, and decreases in serum Na^+ or K^+ levels were corrected. The seventh day was the study end-point.

Data were computerized and an SPSS statistical program was used. The Kolomogorov-Smirnov goodness of fit was used to test normality of data. Parametric data were displayed as mean ± SD. Nonparametric data were subjected to Kruskal-Wallis and Mann-Whitney U tests. The former was used to define median (25th to 75th percentile) values for each variable of all groups. Statistically significant differences of variables were tested once more for individual groups by the Mann-Whitney U test. A value of $P < 0.05$ was selected as a minimum for significance.

Results

The demographic data and operative times are shown in Table 1. Acute hemodilution did not result in significant hemodynamic disruption or result in detectable end-organ or stress-hormone changes when compared to control patients. A comparison of AH, when performed in awake patients and after induction of anesthesia, revealed changes in hemodynamic, coagulation, and hormonal variables. AH in awake patients was associated with higher values of heart rate and mean arterial blood pressure than those measured in anesthetized patients (Table 2). Similarly, the coagulation variables demonstrated higher levels of prothrombin activity and platelet counts after AH in conscious patients than in the anesthetized group (Table 3). The median serum prolactin level, after AH, was higher in the anesthetized group than in awake patients (Table 4).

At the end of surgery, the control group displayed higher serum Na^+ levels than the AH awake patients (Table 3), whereas the hematocrit was significantly lower in the third group (Table 2). Other variables did not display any significant difference between hemodiluted and control patients.

On the third postoperative day, the control serum K^+ was lower than the third group, whereas it was near to being significantly lower ($P = 0.05$) than the second group (Table 3). This was reversed on the seventh day where serum K^+ was higher in the control than the AH patients. The control prothrombin activity measured on the third day was lower than that of AH patients (Table 3), while the control serum bilirubin concentrations were higher during the third and seventh postoperative days (Table 5).

The third group, in which AH was carried out after induction of anesthesia, showed preoperative higher levels of serum alkaline phosphatase and a reversed albumin/globulin ratio. These were reported further on the third and seventh postoperative days (Table 5).

During the postoperative period, none of the AH patients were reexamined for bleeding or required ho-

Table 2. Perioperative Hemodynamic and Hematologic Median Variables of Patients Subjected to Acute Hemodilution and Radical Cystectomy

	Heart rate (beats/min)			Central venous pressure (cm saline)			Mean arterial blood pressure (mm Hg)			Hemoglobin ($g \cdot dL^{-1}$)			Hematocrit (%)		
	I*	II*	III*	I	II	III	I	II	III	I	II	III	I	II	III
Before anesthesia	80	82	78	5.0	5.0	4.5	103	97	93	12.3	12.7	13.9	43	46	43
After hemodilution		97†	71	—‡	8.0	8.5	—	105†	89	—	10.1	10.4	—	36	34
End of surgery	88	87	86	6.0	6.0	5.5	98	94	93	11.6	11.0	10.8	43§	42†	36
Third postoperative day	85	84	88	—	—	—	95	93	93	9.9	9.5	10.0	36	33	33
Seventh postoperative day	83	84	86	—	—	—	93	93	93	10.0	9.0	9.8	35	33	34

Significance level $P < 0.05$.
* Group I = control; Group II = preinduction hemodilution; Group III = postinduction hemodilution.
† Significant difference between II and III.
‡ — Was not done.
§ Significant difference between I and III.

Table 3. Perioperative Serum Electrolytes and Coagulation Median Variables in Patients Subjected to Acute Hemodilution and Radical Cystectomy

	Sodium ($mM \cdot L^{-1}$)			Potassium ($mM \cdot L^{-1}$)			Prothrombin activity (%)			Fibrinogen concentration ($mg \cdot dL^{-1}$)			Platelet count (10^3) (counts/mm^3)		
	I*	II*	III*	I	II	III	I	II	III	I	II	III	I	II	III
Before anesthesia	141	142	140	3.7	3.6	3.9	91	98	94	413	433	431	208.0	244.5	216.5
After hemodilution	—†	139	138	—	3.6	3.5	—	87‡	79	—	372	332	—	238.0‡	204.5
End of surgery	135§	132	133	3.6	3.7	3.8	—	—	—	—	—	—	—	—	—
Third postoperative day	138	137	137	3.5¶	3.7	3.8	72§	91	86	428	525	474	202.5	246.5	203.5
Seventh postoperative day	136	137	139	4.0§	3.5	3.8	—	—	—	—	—	—	—	—	—

Significance level $P < 0.05$.
* Group I = control; Group II = preinduction hemodilution; Group III = postinduction hemodilution.
† — Was not done.
‡ Significant difference between II and III.
§ Significant difference between I and II.
¶ Significant difference between I and III.

Table 4. Median Serum Hormonal Changes in Patients Subjected to Acute Hemodilution and Radical Cystectomy

	Cortisol ($\mu g \cdot dL^{-1}$)			Prolactin ($ng \cdot mL^{-1}$)			Growth hormone ($ng \cdot mL^{-1}$)		
	I*	II*	III*	I	II	III	I	II	III
Before anesthesia	20.0	21.4	34.6	12.8	6.7	12.7	1.0	0.6	0.3
After hemodilution	—†	14.9	18.3	—	7.9‡	26.9	—	1.3	2.5
End of surgery	28.6	33.1	30.0	12.3	13.1	16.4	2.0	2.2	1.3

Significance level $P < 0.05$.
* Group I = control; Group II = preinduction hemodilution; Group III = postinduction hemodilution.
† — Was not performed.
‡ Significant difference between II and III.

mologous blood transfusion to compensate for bleeding or for severely low hemoglobin or hematocrit. There was no clinical or biochemical evidence that organs had been affected by AH.

Discussion

The stress response is a state produced by many factors, including general anesthesia and surgery (4). It is mediated by the hypothalamus and manifested through the sympathetic nervous system and the endocrine glands. Estimations of the circulating hormonal and humoral levels constitute the prominent direct markers of a stressful state, whereas hemodynamic changes and alterations in blood glucose levels are the main indirect markers of a stress response.

It became generally accepted that increased activity of the adrenal cortex is an essential part of the body's response to stress. Cortisol is the main corticosteroid in man and may be increased enormously in stress (5). Prolactin, a pituitary hormone, is regarded as a trauma or stress hormone (6) and increases in many situations

Table 5. Hepatic Function Profile Before and After Acute Hemodilution and Radical Cystectomy

	Before anesthesia			Third day			Seventh day		
	I*	II*	III*	I	II	III	I	II	III
Bilirubin ($mg \cdot dL^{-1}$)	0.7	0.6	0.6	0.8† ‡	0.5	0.6	0.8† ‡	0.4	0.5
Aspartate aminotransferase ($IU \cdot L^{-1}$)	18	19	19	24	19	19	26	20	16
Alanine aminotransferase ($IU \cdot L^{-1}$)	34	27	23	40	39	35	34	34	29
Alkaline phosphatase ($IU \cdot L^{-1}$)	42‡	41§	81	30† ‡	23§	55	30‡	26§	58
Albumin ($g \cdot dL^{-1}$)	4.3‡	4.1§	3.8	3.1‡	2.9§	2.3	3.1‡	3.2§	2.5
Globulin ($g \cdot dL^{-1}$)	2.8‡	3.2§	4.6	2.2‡	2.5§	3.1	2.2‡	2.5§	3.9

Significance level $P < 0.05$. Values are in median.
* Group I = control; Group II = preinduction hemodilution; Group III = postinduction hemodilution.
† Significant difference between I and II.
‡ Significant difference between I and III.
§ Significant difference between II and III.

which have elements in common with stress (4). Growth hormone, another pituitary hormone, is not always released in less complex and traumatic procedures, but situations reflecting a demand for oxidizable substances are probably the principal stimuli for its release (4).

Acute hemodilution, in this magnitude, is not a stress-producing technique when performed in the awake patient and is not associated with significant changes in measured serum hormones. The associated hyperdynamic state, manifested by increases in heart rate and mean arterial blood pressure, may be attributed to emotional distress caused by the withdrawal of blood from an awake patient, or by a response to AH caused by an increase in sympathetic nervous activity, particularly at the level of β-adrenergic receptors (7). However, performing more aggressive hemodilution through the withdrawal of 3 or more units of blood may trigger the stress response.

The differential response of the estimated hormones after induction of anesthesia and AH is not unexpected. Growth hormone does not increase following gastroscopy and proctoscopy and demonstrates a delayed peak during surgery (4). Prolactin is an important direct marker of a stress response (4,6) and could be considered as a broad-spectrum direct marker of a stressful state. The lack of data on serum concentration profile of the secreted cortisol makes it unsafe to speculate the lack of increase in the estimated level. The fast feedback inhibition of the secretion of adrenocorticotropic hormones which occurs within minutes of cortisol secretion (8) and the lack of surgical stimuli during the technique of hemodilution could possibly be contributing factors.

The association of epidural block, general anesthesia, and AH may interact to influence the cardiovascular system through modifications of venous return and sympathetic nervous activity. AH increases sympathetic activity (7) and venous return, whereas epidural block increases venous distensibility (9) and decreases venous return (10) and sympathetic nervous activity. These factors may explain hemodynamic stability following AH after lumbar epidural block and general anesthesia, whether the diluting solution is either colloid (3) or crystalloid, as reported in this study.

Transient dilution of coagulation factors occurs during AH. These variables regain their preoperative values after transfusion of autologous blood. These changes have been reported previously (2). The increased prothrombin activity in hemodiluted patients during the postoperative period may necessitate proper anti-thrombosis prophylaxis. It is noteworthy that none of AH patients were reexamined for bleeding or required homologous blood transfusion to compensate for alarmingly low hemoglobin or hematocrit.

Preinduction AH was associated with higher levels of prothrombin activity and platelet count than those reported in postinduction hemodiluted patients. The explanation of this difference is not clear, but emotional distress can induce activation of coagulation. This could have a salutary effect in clinical settings with preoperative low levels of these coagulation variables.

The postoperative decrease in serum bilirubin level of AH patients may be a dilutional effect. Postinduction AH patients demonstrated a preoperative increase in serum alkaline phosphatase with a reversal of the albumin to globulin ratio. Operative inspection of the liver, a routine during this surgery, did not reveal hepatic metastasis or evidence of biliary obstruction, and the postoperative transaminase levels were within normal range.

The limitations of this study are the lack of data on hemodynamic profile and on oxygen availability. Since it is a technique without stress effect, AH can be used in patients with limited cardiac reserve, and patients with hemoglobin $< 10\ g \cdot dL^{-1}$. This may expedite its use especially when homologous blood is undesirable or not available.

In conclusion, acute hemodilution is not a stress-producing technique. Its combination with lumbar

epidural and general anesthesia is associated with hemodynamic stability and has no deleterious effect on organ function.

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