Vasopressin Levels

in

Major Head and Neck Surgery

Niels F. Jensen, M.D.[1]
Robert I. Block, Ph. D.[2]

[1] Assistant Professor, Department of Anesthesia, University of Iowa College of Medicine (NFJ)
[2] Associate Professor, Department of Anesthesia, University of Iowa College of Medicine (RIB)

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Corresponding author:

Address correspondence to Dr. Jensen, Department of Anesthesiology, University of Iowa College of Medicine, Iowa City, Iowa 52242. Telephone (319) 356-2633, FAX 319-356-2940. No reprints available.

Abbreviations:

Argonine vasopressin (AVP); Anti-diuretic hormone (ADH); Central venous pressure (CVP) monitoring

Key words:

Anti-diuretic hormone; Vasopressin; Central venous pressure monitoring

ABSTRACT

Study Objective:

In an effort to further understand the perioperative intravascular volume status of major head and neck surgery patients, serum antiduretic hormone (ADH) and osmolality levels were assessed at four perioperative periods.

Design:

Random, major head and neck surgical patients.

Patients:

Thirty-five

Interventions:

Placement of central venous pressure monitor; obtained serum osmolaltiy and serum vasopressin levels at four period perioperatively.

Measurements and Main Results:

ADH levels were lower both after patients were anesthetized and five hours into the procedure than at either baseline or 24 hours after the end of the procedure. ADH levels after patients were anesthetized did not differ from those at five hours into the procedure, nor did ADH levels at baseline differ from those 24 hours after the end of the procedure. In addition, osmolality levels did not change over time.

Additional analyses examining relationships of preoperative, intraoperative, and postoperative characteristics to ADH levels after patients were anesthetized and five hours into the procedure, as well as changes from baseline at these times and the baseline levels themselves, detected no significant relationships.

Conclusions:

This study provides information about the perioperative intravascular volume status of major and head surgery patients which may be important to intraoperative care--especially to decisions regarding invasive intraoperative fluid monitoring. Specifically, the data provide additional evidence against the routine placement of central venous catheters to guide fluid administration during major head and neck surgery.

INTRODUCTION

While precise information is not available, the use of central venous monitors to assess intraoperative fluid status during major head and neck is quite common. This study was undertaken to evaluate osmolality and arginine vasopressin (AVP or ADH) levels during the course of major head and neck surgery. It represents an ongoing effort to determine intravascular fluid status and thereby to provide information about the efficacy of invasive intravascular fluid monitoring during such surgery. Previous work suggested no correlation between the presence and absence of central venous pressure (CVP) monitoring and a number of related variables, including total intravenous fluid administration, during these lengthy and sometimes bloody procedures. (1) We felt that perhaps serum osmolality and vasopressin may reveal subtle differences in volume status between patients with and without central venous pressure monitoring which were not detected in the previous work and that perhaps these differences may correlate to such other important perioperative parameters as total urine output, oliguria, and hypotension. The absence of such differences would cast more doubt upon the routine placement of a central venous catheter to guide fluid administration during major head and neck surgery.

MATERIALS AND METHODS

This study was approved through the Human Studies Committee at the University of Iowa Hospitals and Clinics.

Thirty-five patients undergoing elective major head and neck surgery at the University of Iowa Hospitals and Clinics during 1991-92 were studied. Major head and neck surgery was defined as a procedure with a minimum duration of four hours and an expected blood loss equal to or greater than 500 ml. The large majority of these surgeries involved head and neck cancer resection and reconstruction, for example radical neck dissection with a pectoralis major myocutaneous flap for resection of a pyriform sinus malignacy. Patients were selected for inclusion in the study on the basis of the procedure performed, not the planned use of central monitoring; the use of a central venous catheter was not a criteria for selection and no attempt was made prior to selection to determine if a central venous catheter was planned.

For consenting patients meeting the above criteria of planned major head and neck surgery, ADH and osmolality levels were measured at four times: at baseline, i.e., the night before surgery; after patients were anesthetized, but before surgical incision; five hours into the procedure; and 24 hours after the end of the procedure. Additional preoperative, intraoperative, and postoperative variables were recorded, as follows:

Preoperative Variables: Preoperative data recorded for each patient included age, sex, weight, and BUN, creatinine, and hemoglobin levels within a week prior to surgery. In addition, the presence of past cardiac, renal, or pulmonary disease, as defined below, was noted.

Intraoperative Variables: Data extracted from the intraoperative records included surgical duration from incision to final suture placement, utilization of a nitrous oxide/isoflurane/fentanyl or other anesthetic technique, estimated blood loss, lowest hourly intraoperative urine output in ml, presence of intraoperative oliguria (defined as a urine output of less than 0.5 ml/kg/hr at one or more hourly intervals throughout surgery), total intraoperative urine output in ml, total intraoperative administration of blood, colloid, and crystalloid, the presence of one or more recorded systolic blood

pressures under 70 mm Hg at any time following incision, intraoperative levels of hemoglobin, use of a central monitor, and initial central venous pressure.

Postoperative Variables: Data from the postoperative period included total postsurgical intensive care unit and hospital days, hemoglobin levels on postoperative day one, BUN and creatinine levels on postoperative days one and two, total urine output from postoperative days 1-3, oliguria (any hourly urine output on postoperative days 1-3 of less than 0.5 cc/kg/hr), wound dehiscence (abnormal early surgical wound breakdown), or death during the postoperative period of hospitalization. In addition, we evaluated records for the occurrence of pneumonia and pulmonary edema. We did not attempt to independently define criteria for these, but rather relied upon notations provided by the surgical and intensive care unit teams and consultants. We made no attempt to judge the validity of the diagnosis made.

Statistical Analyses: ADH and osmolality levels at baseline, after patients were anesthetized but prior to surgical incision, five hours into the procedure, and 24 hours after the end of the procedure were submitted to one-way analyses of variance examining changes over time. Significant effects in these analyses were clarified by pairwise comparisons of the four times of measurement, using Duncan's Multiple Range Test. A significance level of $p < 0.05$ was used for all tests. Levels at times differing significantly from baseline, as well as changes from baseline at these times and the baseline levels themselves, were included in additional analyses examining relationships to other preoperative, intraoperative, and postoperative characteristics. These analyses consisted of Pearson product-moment correlations with quantitative variables such as age and t tests for dichotomous characteristics such as gender. The significance level for these additional analyses was adjusted for the number of variables analyzed, using Bonferroni's method.

Assay: Plasma was obtained from iced, heparinized blood samples and stored at -20°C until processed. Plasma proteins were initially precipitated with cold acetone. The acetone was extracted with cold petroleum ether, the phases separated by centrifugation and the ether phase discarded. The lower phase containing the AVP was taken to dryness and stored at -20°C until assay.

The AVP RIA utilizes a nonequilibrium technique wherin antibody and cold standards (Pennisula Labs, Belmont, CA) or sample extracts (diluted in acidic saline) were pre-incubated overnight and the ^{125}I AVP (New England Nuclear, Boston, MA) added on the second day(2) . After an additional overnight incubation, the antibody-bound AVP was precipitated by the polyethylene glycol separation technique (PEG 8000, 12.5%). AVP assay buffer used to dilute antibody and tracer is 0.05 M Tris, pH 8.0, 0.01 M Na_2EDTA, 0.01% NaN_3 containing 0.1% BSA.

Assay Sensitivity: The assay detection limit for standard AVP is 0.24 units (or 0.58 pg). Taking into account the extraction efficiency (78%) and the volumes for extract added to the RIA (100 ul, 150 ul, and 200 ul), this corresponds to a plasma detection level of 1.5 uU / ml (or 3.6 pg / ml). Sensitivity is not a limiting factor if greater than 1 ml of plasma is available for extraction and concentration.

RESULTS

Of the 35 patients who participated, 20 were men and 15 were women. A nitrous oxide / isoflurane / fentanyl anesthetic technique was used with 83% of patients.

Initial central venous pressures were available only for patients in whom central monitors were placed (46% of the patients). Missing data rates were 11% for postoperative oliguria; 17% for total urine output from postoperative days 1-3; 18% for ADH levels; 20% for intraoperative hemoglobin levels and BUN and creatinine levels on the second postoperative day; 23% for osmolality levels; and under 3% for all other variables.

ADH levels are shown in Figure 1. The levels changed over time, $F(3, 111) = 6.1$, $p < 0.001$. Duncan's Test indicated that ADH levels were lower both after patients were anesthetized and five hours into the procedure than at either baseline or 24 hours after the end of the procedure. ADH levels after patients were anesthetized did not differ from those at five hours into the procedure, nor did ADH levels at baseline differ from those 24 hours after the end of the procedure.

Osmolality levels did not change over time, $F(3, 104) < 1$. Mean (± standard deviation) osmolality levels were 291.0 ± 9.1, 291.9 ± 6.7, 292.2 ± 7.0, and 292.6 ± 5.5 mosm / l at baseline, after patients were anesthetized, five hours into the procedure, and 24 hours after the end of the procedure, respectively.

The additional analyses examining relationships of preoperative, intraoperative, and postoperative characteristics to ADH levels after patients were anesthetized and five hours into the procedure, as well as changes from baseline at these times and the baseline levels themselves, detected no significant relationships. In particular, ADH levels did not differ in patients with and without central venous pressure monitoring. (It was not feasible to do t tests for postoperative death, because only one person died.) The results with respect to ADH levels after patients were anesthetized are provided in Tables 1 and 2. Table 1 shows correlations with quantitative variables such as age and Table 2 shows t tests for dichotomous characteristics such as central venous pressure monitoring.

Use of Bonferroni's method to adjust the significance level in these additional analyses for the large number of variables that were considered led to very conservative tests, raising the possibility that some meaningful, but modest, relationships of preoperative, intraoperative, or postoperative characteristics to ADH levels might have been missed. In fact, this did not appear to be the case. Examination of those correlations and t tests that reached a $p < 0.05$ significance level prior to adjustment by Bonferroni's method indicated that none reflected a physiologically or clinically meaningful, convincing relationship of ADH levels to any other characteristic. The relationships were counterintuitive and/or based on very few patients; they were presumably spurious, i.e., potential Type 1 errors that were avoided by use of Bonferroni's method.

For example, the strongest correlation in Table 1 reflected a tendency for higher ADH levels after patients were anesthetized, compared to lower levels, to be associated with longer postoperative hospital stays; but examination of the data indicated that one particular patient contributed greatly to this correlation. This patient had the longest postoperative hospital stay (105 days) and the highest ADH level after being anesthetized (23.52 pg/ml), as well as the second highest ADH level at baseline (37.54 pg/ml). As another example, the t value of largest magnitude in Table 2 reflected a tendency for patients with histories of significant renal disease to have higher levels of ADH after being anesthetized than those without such histories; but this difference was based on data for only two patients with histories of significant renal disease. Thus, neither the strongest correlation in Table 1, nor the t value of largest magnitude in Table 2, appeared to reflect a meaningful, convincing relationship of ADH levels after being anesthetized to another characteristic.

DISCUSSION

The osmoreceptor-antidiuretic hormone system is a very powerful mechanism for controlling extracellular fluid osmolality. Extracellular fluid osmolality averages almost exactly 300 mOsm/liter. To appreciate how tightly this is controlled, one only needs to be reminded that this rarely changes more than 3 per cent. While altered by anesthesia and surgery (see below), the osmoreceptor-antidiuretic hormone system is the most important control system for extracellular osmolality intraoperatively. The other two mechanisms, thirst and salt appetite, are not operational.

The osmoreceptor-antidiuretic hormone system is a feedback control system. An increase in serum osmolality stimulates osmoreceptors located in the supraoptic nucleus of the hypothalamus to release ADH. ADH increases the permeablity of the distal tubules and collecting ducts to water and therefore results in water conservation by the kidney. This conservation of water, accompanied by the loss of sodium and other osmotically active substances in the urine, corrects concentrated extracellular fluid. Conversely, hypoosmolarity results in less stimulation of osmoreceptors, less secretion of ADH, and less absorption of free water by the kidney--as extracellular fluid is concentrated back toward normal. (3)

Central venous catheters are typically placed to assist in the assessment of cardiac function and intravascular volume status (as measured by right ventricular filling pressures), to provide secure intravenous access, and to allow vasoactive drugs to be delivered directly into the central circulation. (1) CVP monitoring is frequently employed in major head and neck surgery, particularly in patients with malignancies. It is not known precisely how routinely this is done but in a random evaluation of over 100 charts at the University of Iowa Hospitals, placement of a CVP monitor during major head and neck surgery occurred in approximately 50% of cases. The most frequent reason for CVP catheter placement in the setting of this type of surgery is to facilitate fluid assessment during these lengthy and sometimes bloody procedures. Specifically, it is felt by many anesthesiologists that a CVP catheter will result in more rational, appropriate, and judicious fluid administration. Better fluid and volume management should be associated with greater intraoperative and postoperative hemodynamic stability and fewer complications such as hypotension and oliguria, pulmonary edema, congestive

heart failure, myocardial infarction, and renal failure. In fact, our data suggest that patients undergoing major head and neck surgery do not appear to be fluid depleted and/or hyperosmolar perioperatively and the routine placement of central venous monitors to guide fluid administration on these grounds may not be warranted.

Previous work suggested that use of central venous monitoring to provide a gauge for fluid and blood replacement during major head and neck surgery did not alter the amount of total intravenous fluid or blood administered. (1) An array of preoperative, intraoperative, and postoperative parameters also did not differ between those receiving and not receiving a central venous monitor during this type of procedure. The conclusion regarding volume replacement is an especially important one because, as noted, concerns about intravascular volume status during such long surgery often serve as the basis for the placement of the monitor.

Since differences in the type and volume of intravenous fluid administered in patients with or without central monitoring were not detected in our previous study, we examined changes in vasopressin and osmolality levels during the perioperative period. If vasopressin and/or osmolality levels changed over time, these changes might vary in patients with and without central venous pressure monitoring, be associated with differences in perioperative volume status and fluid management, or modulate the effects of central venous pressure monitoring on perioperative volume status and fluid management. In fact, osmolality levels did not change over time. After patients were anesthetized and five hours into the procedure, ADH levels were lower than at baseline or 24 hours after the end of the procedure, but these levels were not significantly related to central venous pressure monitoring or any other perioperative characteristic. Osmolality levels did not change significantly over time.

There are a number of factors which stimuate the secretion of ADH. Increased plasma osmolality is only one of them. (4) Others include decreases in circulating blood volume, reductions in mean arterial or left atrial pressure(5) , catecholamines, angiotensin II, atrial natriuretic peptide(5) , and surgical stress. Vasopressin is thought to be a particularly sensitive marker of surgical stress. (4)

The baseline and postoperative elevation in ADH level is not unexpected, but the fact that it was not associated with increased osmolality is interesting. One might expect for example that

patients presenting for major head and neck cancer surgery, often dysphagic and even cachexic, would be hyperosmolar and that this may might lead to elevated ADH levels. In addition, given the extent of surgery and ongoing fluid shifts and extravasation into the surgical wound during and following completion of surgery, one might again anticipate possible hypovolemia and hyperosmolality. Neither of these appear to occur. Further, the relative elevation of ADH at baseline and 24 hours postoperatively cannot be explained on the basis of osmolality changes.

The relative elevation of ADH at baseline and 24 hours postoperatively may be due a variety of factors not evaluated in this study. It is known, for example, that both psychological and surgical stress raise ADH levels. (4) (6) The former may relate to the preoperative ADH elevation observed and the later to the postoperative elevation found. In addition, fentanyl has been demonstrated to block ADH increases during coronary artery bypass grafting. (7) The importance of narcotic modulation of ADH response is difficult to assess in this study since all patients studied received fentanyl during or shortly after the induction of anesthesia. All anesthetics do not appear to have this effect of modulation of ADH release. For example, the use of inactin prior to decapitation in rats does not prevent a dramatic rise in ADH. (8)

Despite a wealth of information on the timing(9) (10) , insertion sites and techniques(11) (12) (13, 14) , and complications (15) (16-25) (26) associated central venous catheter placement, there is very little understanding of the degree to which the benefits of CVP monitors in routine surgery outweigh the risks and costs.

The scientific foundations of efficacy in many if not most health care areas is simply not known. (27) According to the Institute of Medicine, valid randomized controlled efficacy studies have been applied to only a very small part of medical practice. (28) Eddy examined many well-accepted conventional treatments to learn if valid efficacy studies exist regarding recommended practice or alternative managements. He concluded that virtually none have been evaluated with well-designed, controlled studies comparing alternative interventions. (27) It appears that many "standard" diagnostic and therapeutic practices, involving huge numbers of patients, high risks, and tremendous costs, rest upon very uncertain foundations with respect to efficacy.

(29)

With the results of this study coupled with that cited above, it appears that this may be the case with respect to the routine placement of central venous catheters for major head and neck surgery.

CONCLUSION

This study represents an ongoing effort to judge the efficacy of a common medical procedure, the placement of routine central venous monitoring in major head and neck surgery. It suggests that patients undergoing major head and neck surgery are not fluid depleted and/or hyperosmolar intraoperatively and that the routine placement of central venous monitors to guide fluid administration for prevention of these conditions may not be warranted. If this can be further substantiated, it may be possible to reduce the considerable risks and costs associated with the routine placement of central venous catheters for major head and neck surgery.

Table 1

Quantitative Preoperative, Intraoperative,

and Postoperative Variables: Means and Correlations with

ADH Levels After Patients were Anesthetized, but Before Surgery

	Mean ± SD	r with ADH
Preoperative		
Age (yr)	56 ± 16	0.24
Weight (kg)	74 ± 19	0.07
Osmolality the night before surgery (mosm/l)	291 ± 9	0.37
Hemoglobin (gm/dl)	14 ± 2	-0.16
Intraoperative		
Duration (min)	673 ± 216	-0.27
Osmolality after patients were anesthetized, but before surgery (mosm/l)	292 ± 7	0.004
Osmolality five hours into the procedure (mosm/l)	292 ± 7	0.09
Hemoglobin (gm/dl)	10 ± 2	0.13
Blood loss (cc)	842 ± 511	-0.39
Replacement blood (cc)	187 ± 246	0.11
Replacement crystalloid (cc)	5,157 ± 1,845	-0.37
Replacement colloid (cc)	650 ± 879	-0.23

Table 1 (continued)

	Mean ± SD			r with ADH
Total urine output (cc)	1,230	±	894	-0.27
Lowest urine output per hr (cc)	27	±	12	-0.24
Initial centrous venous pressure (mm Hg)	11	±	4	0.26
Postoperative				
Surgical intensive care unit stay (days)	4	±	7	0.06
Hospital stay (days)	23	±	24	0.48
Osmolality 24 hrs after end of procedure (mosm/l)	293	±	6	0.47
Hemoglobin, day 1 (gm/dl)	10	±	2	0.26
Total urine output, days 1-3 (cc)	5,761	±	2,496	0.13

Note: None of the correlations was significant after adjusting for the number of variables analyzed (see text). SD = standard deviation.

Table 2

Dichotomous Preoperative, Intraoperative, and Postoperative Characteristics: Relationships to ADH Levels After Patients were Anesthetized, but Before Surgery

	Percentage with Characteristic Present	ADH (μ units/ml) Mean ± SD with Characteristic Present	ADH (μ units/ml) Mean ± SD with Characteristic Absent	t
Preoperative				
Male gender	62	2.6 ± 2.0	4.2 ± 3.1	1.7
Past cardiac dysfunction	10	1.4 ± 1.0	3.5 ± 2.6	1.4
Past pulmonary dysfunction	69	3.5 ± 2.3	2.6 ± 2.9	-1.0
Past renal dysfunction	7	6.7 ± 3.7	3.0 ± 2.3	-2.1
Cardiac medications	52	3.8 ± 2.9	2.7 ± 2.0	-1.2
Other medications	48	3.4 ± 3.1	3.1 ± 2.0	-0.3
Intraoperative				
Nitrous oxide/isoflurane/fentanyl anesthetic	83	3.3 ± 2.6	3.2 ± 2.2	-0.1
Central monitor	52	3.1 ± 2.8	3.4 ± 2.2	0.2
Oliguria (< 0.5 cc/kg/hr)	76	3.5 ± 2.7	2.5 ± 2.0	-0.9
Systolic blood pressure < 70	7	4.8 ± 0.7	3.1 ± 2.6	-0.9

Table 2 (continued)

	Percentage with Characteristic Present	ADH (μ units/ml) Mean ± SD with Characteristic Present	ADH (μ units/ml) Mean ± SD with Characteristic Absent	t
		Postoperative		
Oliguria (< 0.5 cc/kg/hr)	36	3.0 ± 3.8	3.8 ± 1.7	0.6
Wound dehiscence	7	4.6 ± 1.0	3.1 ± 2.6	-0.8
Pulmonary edema	10	2.1 ± 2.1	3.4 ± 2.6	0.8
Pneumonia	14	3.0 ± 1.6	3.3 ± 2.7	0.2

Note: ADH levels after patients were anesthetized were missing for 17% of patients. None of the t values was significant after adjusting for the number of variables analyzed (see text). SD = standard deviation.

Figure Captions

Fig. 1. Change in ADH levels over time. B = baseline, i.e., the night before surgery; 1 = after patients were anesthetized, but before surgery; 2 = five hours into the procedure; 3 = 24 hours after the end of the procedure. Error bars indicate one standard deviation. Differences according to Duncan's Test, $p < 0.05$, are indicated as follows: * Differs from baseline levels; † Differs from levels 24 hours after the end of the procedure.

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