Renin-aldosterone system alterations during abdominal gynaecological operations under general or combined general and epidural anaesthesia

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Summary

Alterations of plasma renin-activity and aldosterone levels were comparatively studied in 41 premenopausal patients who were subjected to total abdominal hysterectomy. Twenty-one women received general anaesthesia (group A) and 20 received a combination of general and epidural anaesthesia (group B). Five blood specimens were drawn from each patient in order to determine plasma aldosterone levels (PA) and plasma renin activity (PRA) by radioimmunoassay (RIA).

The rise of PA levels in group A occurred 30 min after the initiation of surgery and at that time there was a statistically significant difference as compared with the epidural anaesthesia (EA) group ($p<0.001$). PRA levels in both groups showed a rise of limited statistical significance at 30 minutes after the initiation of surgery ($p<0.05$). During the remaining time intervals, group A did not show any significant changes, whereas group B showed a reduction of limited statistical significance ($p<0.05$).

General anaesthesia for gynecological abdominal surgery without the use of volatile agents significantly increases plasma aldosterone levels. Combined anaesthesia does not totally inhibit intraoperative hyperaldosteroism but it is much slower and is of great advantage for the patient.

Introduction

The renin-angiotensin-aldosterone system is an important factor in aldosterone secretion. It is also a potent vasoconstrictive factor, which together with vasopressin constitutes an important mechanism for the maintenance of circulatory homeostasis in the body. These mechanisms start in emergency situations such as haemorrhage, dehydration, diuretic therapy, upright position, etc. Their action, however, is enhanced after an extensive blockade of the sympathetic nervous system if the sympathetic blockade is achieved by epidural blockade or by means of drugs, such as reserpine and metyrosine [1, 2, 3]. It has also been determined that angiotensin II induces and potentiates the release of catecholamines [4]. The atrial natriuretic peptide (ANP) exerts an inhibitory effect on the secretion of both renin and aldosterone [5, 6]. In the past few years, there has been increasing interest on the study of the extrarenal renin production and its role in the physiology of other systems and mainly in the reproductive system [6-9].

The aim of this study was to compare the effect of two types of anaesthesia (general and combined general and epidural anaesthesia) in lower abdominal surgery on the renin-aldosterone system and to determine the preferred anaesthetic method in order to avoid hyperaldosteronism.

Materials and Methods

The study was carried out in 41 premenopausal women who showed no signs of endocrine, cardiovascular, hepatic, renal or any other form of disease (ASA grade I), under normal dietary sodium intake. All the patients gave their written consent and the study had the approval of the University Ethical Committee. The patients were subjected to total abdominal hysterectomy and were randomly allocated into two separate groups, regarding the type of anaesthesia administered. Twenty-one patients were given general anaesthesia (group A) and 20 patients were given combined general and epidural anaesthesia (group B).

The type of general anaesthesia administered to both groups was identical. Initially, each patient received 1 mg midazolam and 2 μg/Kg of Fentanyl IV; 4 mg/Kg thiopental and 0.08 mg/Kg pancuronium bromide for the induction of anaesthesia. Controlled ventilation with 100% oxygen using a face mask was given for 2 minutes, followed by tracheal intubation using an 8 mm cuffed endotracheal tube under direct laryngoscopy. Anaesthesia was maintained with nitrous oxide/oxygen (3:1) and 2 μg/Kg Fentanyl IV. No volatile anaesthetic agent was used. The latter was administered five minutes prior to the skin incision.

Fentanyl IV was administered 60 min after the procedure had started. Prior to the administration of general anaesthesia to patients in group B an epidural block was performed by lumbar puncture (at the level of L_3-L_4 or L_2-L_3), using a 16G Tuohy needle with a plastic catheter. A volume of 16 ml bupivacaine 05% injected through the catheter without adrenaline was required to achieve epidural block from T_4 as far as the S_5 neurotome. It was necessary to ensure a T_4 block to secure a sympathectomy. This volume was calculated according to the patient's height [10]. Blocking efficacy was tested by pin prick 20 minutes after the administration of the local anaesthetic agent. If the block was satisfactory, we proceeded to administer general anaesthesia. If the block did not prove to be completely satisfactory, this particular patient was excluded from the study.

The intravenous infusion of Ringer's lactate solution was identical for both groups of patients (i.e. same volumes at same time intervals). During the procedure, five blood samples were

Revised manuscript accepted for publication December 20, 1999

drawn from a separate vein from each patient; the plasma renin activity levels (PRA) and the plasma aldosterone levels (PA) were measured in the following time intervals: before anaesthetic (sample BA), 10 minutes prior to initiation of any anaesthetic procedure (sample A), 10 minutes after the establishment of general anaesthesia and just before the skin incision in both groups (sample B), 30 minutes after the initiation of the operation (sample C), 60 minutes (D), and 120 minutes (E) after initiation of the operation.

Plasma aldosterone measurement was performed by radioimmunoassay (RIA) using the commercially available kit "RSL (125) Aldosterone". Plasma renin activity (PRA) was measured by RIA, using the commercially available kit Renin-RIA Bead.

The Student's t-test was used to compare the demographic and clinical features of the patients. Evaluation of the changes in every parameter at different intervals for each group was achieved by applying the One-Way ANOVA method (analysis of the variability). The difference between the two groups at various time intervals was studied by the Two-Way ANOVA (analysis of the variability) method, where $p<0.05$ was considered as indicative of statistical significance.

Results

Patient data are given in Table 1. There was no significant difference between the two groups related to their clinical or demographic data, except for the parameter of body weight ($p<0.05$). The latter is not considered essential since the volumes of all regimens administered were calculated according to the patient's body height.

There were no significant differences in mean arterial pressure (MAP) between the two groups, 10 minutes anaesthesia (BA). The changes in MAP during the procedure are shown in Table 2 and Figure 1. Following the establishment of anaesthesia, there was a statistically significant reduction of MAP in both patient groups ($p<0.01$). Thirty minutes after initiation of the operation, the GA group showed a significant rise of MAP ($p<0.01$) which almost reached its preanaesthetic values. At this level, it remained unaltered during the remaining intraoperative intervals (60 and 120 minutes). On the other hand, the MAP in the epidural anaesthesia (EA) group showed no significant change either after the initiation of the operation or during the procedure. Statistically, changes between the two groups were observed at 30 and 60 minutes following initiation of the operation ($p<0.01$ and $p<0.05$, respectively).

There were no significant differences of plasma aldosterone (PA) in preanaesthesia levels between the two groups (Table 3 and Figure 2), or any significant changes in PA levels following the establishment of anaesthesia in both groups. PA levels in the GA group showed an abrupt and significant rise ($p<0.001$) thirty minutes after skin incision, reaching a value three times higher than the preanesthetic value; these levels are significantly different to those observed in the EA group ($p<0.001$), respectively. There were no significant changes in PA levels during the remaining intraoperative time intervals (60 and 120 minutes). PA levels showed a significant rise in the EA group from a 30 to 60 minute time interval. In other words, the rise in PA levels occurred after initiation of operation ($p<0.001$) and remained so through the next intraoperative time interval (120 minutes).

Plasma renin activity (PRA) showed an important dispersion in both groups, at all time intervals (Table 4 and Figure 3); as a result, the changes in PRA observed in each group at various time intervals and the differen-

Table 1. — *Demographic and clinical data of the patients in group A under general anaesthesia (GA) and patients in group B under combined general and epidural anaesthesia (EA).*

	Age (years)		Weight (Kg)		Height (cm)		Duration of operation (minutes)	
Parameter	GA	EA	GA	EA	GA	EA	GA	EA
Mean value	39.4	40.8	67.0*	71.8	162	164	107.4	105.0
Median value	40	42	67	68.5	162	164	108	107
SD**	4.8	4.9	6.2	9.4	4.2	5.6	29.8	15.8
Minimum value	31	29	53	61	153	155	56	84
Maximum value	46	47	81	93	172	175	180	136
Range	15	18	28	32	19	20	124	52

*p<0.05; **Standard deviation

Table 2. — *Mean value, standard deviation and % of change in the mean arterial pressure (mmHg) in relation to the preanaesthetic value (PAV) and blood sample timing.*

Sample timing	No of samples		Mean value of art pressure (mmHg)		SD		% of change in relation to PAV	
(min)	GA	EA	GA	EA	GA	EA	GA	EA
PAV	21	20	97.9	96.5	10.9	6.7	–	–
0	21	20	86.6*	82.6*	9.2	7.6	-11.5	-14.4
30'	21	20	100.7*	81.7	10.7	11.6	2.8	-15.3
60'	21	20	97.9+	84.3	11.0	7.9	0.0	-12.6
120'	21	20	96.0	89.5	9.2	6.9	-1.9	-7.2

*p<0.01; +p<0.05

Table 3. — *Mean value, standard deviation and % of change in plasma aldosterone (ng%) in relation to preanaesthetic values (PAV) and blood sample timing.*

Sample timing	No of samples		Mean value		SD		% of change in relation to BA	
(min)	GA	EA	GA	EA	GA	EA	GA	EA
BA	21	20	6.47	8.31	3.82	5.25	–	–
0	21	20	5.43	7.54	2.24	4.47	-16.1	-9.3
30'	21	20	19.69*	10.41	7.15	7.39	204.3	25.3
60'	21	20	21.35	20.43*	9.10	8.28	230.0	45.8
120'	21	20	21.38	21.69	6.86	10.85	230.4	161.0

*p<0.001

Table 4. — *Mean value, standard deviation and % of change in plasma renin activity (PRA) in relation to the preanaesthetic values (PAV) and blood sample timing.*

Sample timing	No of samples		Mean value of PRA (ng/ml/h)		SD		% of change with regard to PAV	
(min)	GA	EA	GA	EA	GA	EA	GA	EA
BA	21	20	2.34	2.42	1.70	1.41	–	–
0	21	20	2.13	1.64	1.78	1.27	9.0	-32.2
30'	21	20	3.19	2.63*	2.28	2.05	36.3	8.7
60'	21	20	2.52	3.04	1.74	3.34	7.7	25.6
120'	21	20	2.7	1.63	1.85	1.41	15.4	-32.6

*p<0.05

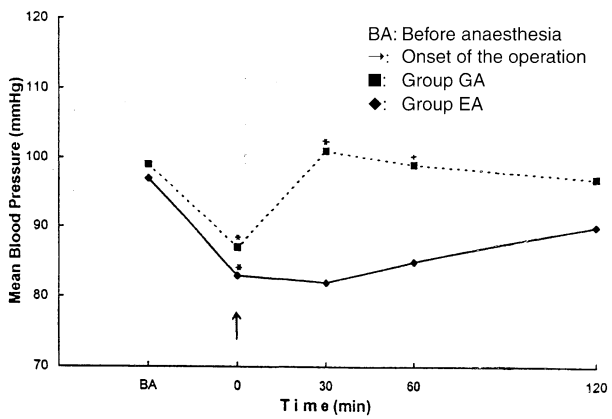

Figure 1. — Changes in mean blood pressure (±SEM) during anaesthesia.

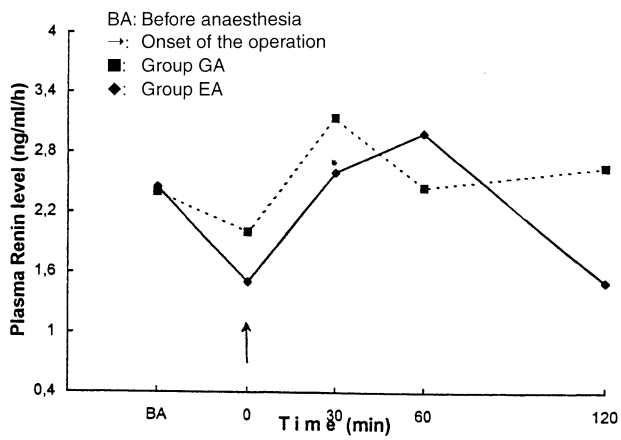

Figure 3. — Changes in renin blood levels during anaesthesia.

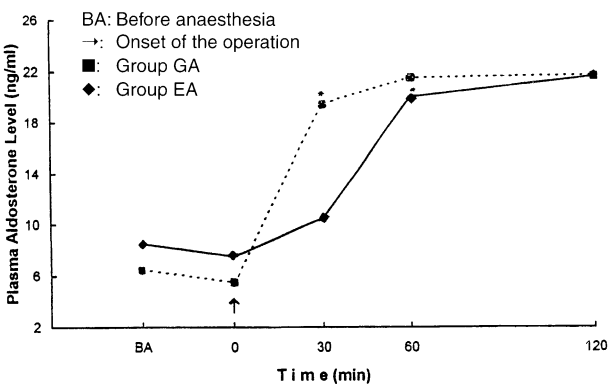

Figure 2. — Changes in aldosterone blood levels (±SEM) during anaesthesia.

ces in PRA between the two groups at the respective time intervals were not statistically significant. Furthermore, statistical evaluation using Scheffe's multiple comparison methods showed that there was a rise in PRA levels in both groups. This rise was of limited statistical significance at 30 minutes after initiation of the operation ($p<0.05$).

During the remaining intraoperative time intervals, the PRA levels in the GA group did not show any significant changes, whereas in the EA group, a reduction of limited statistical significance was noted from the 60 to 120 minute time intervals ($p<0.05$).

To conclude, the PRA values for the GA group did not correlate with the PA values ($r=0.39$, $p<0.00005$, $n=100$).

Discussion

The renin-angiotensin-aldosterone system, through its vasoactive properties (as well as through its effect on sodium reabsorption and potassium excretion by the kidney) appears to be one of the major regulating mechanisms of the circulatory and electrolyte homeostasis in the body. The extent to which anaesthesia and the subsequent operation influence this system and the mechanism involved and how much its function is altered by applying regional anaesthesia are all unknown parameters, since the currently available evidence often contains conflicting views.

Plasma aldosterone increase has been well documented during operative and anaesthetic stress [11-17]. It is not, however, well known which of the anaesthetic techniques is the best in order to suppress hyperaldosteronism. Our results clearly showed that the first significant PA increase appeared at 30 minutes after commencement of surgery in the GA group; in contrast, it appeared at 60 minutes in the EA group. Many authors have observed that under general anaesthesia there is a significant and extensive intraoperative rise in PRA [11-13, 17-19]; this could account for the state of hyperaldosteronism noted. Enquist *et al.* [20] attributes it to the renin-angiotensin-aldosterone system; they came to this assumption after achieving suppression of this system by sodium overloading.

Our study has confirmed an intraoperative rise in PRA level of limited statistical significance ($p<0.05$); this rise was not continuous and stable. In contrast, we observed a concurrent statistically significant increase in PA levels ($p<0.001$). Furthermore, there was no correlation between PRA and PA levels. This disagreement, in regard to other studies already performed, may be attributed to: a) the type of surgical operations which were studied, and b) the administration of a volatile anaesthetic, such as halothane, in sufficient concentrations. A volatile anaesthetic, such as halothane or enflurane, when administered in combination with N_2O, causes a primary rise in PRA, even before skin incision and a secondary rise in PA levels [21]. A probable cause for this rise could be an alteration in renal haemodynamics resulting in the stimulation of the pressure receptors in the juxtaglomerular apparatus. This last remark was confirmed by Seitz *et al.* [15] who noted a rise in PA levels during halothane anaesthesia, even prior to initiation of the operative procedure. The renin-angiotensin aldosterone system plays an important role in the maintenance of circulatory stability during general anaesthesia administered with halothane, since a decrease in smooth muscle tone and a suppressive effect of the adrenergic system has been well documented during this kind of anaesthesia [21]. Thus, we can express our doubts as to whether the renin-angiotensin-aldosterone system plays a definitive role in the induction of intraoperative hyperaldosteronism during the course of general anaesthesia without using halothane or other volatile agents. According to other results, a very strong positive correlation between cortisol and aldosterone rather than renin and aldosterone has been observed [22].

The same observations have been reported by Oyama *et al.* [14] who measured ACTH instead of cortisol levels. They concluded that the contribution of the renin-angiotensin aldosterone system in the hypersecretion of aldosterone during introduction of anaesthesia, at least at the initial stage of the operative procedure, is smaller than the effect of ACTH. Brandt *et al.* [12] reported that epidural anaesthesia extending from T_4 to S_5 neurotome inhibits intraoperative hyperaldosteronism during surgery of the lower abdomen, provided that no intensive and significant drop of arterial pressure occurs. Seitz *et al.* [15] have suggested that a neurotensive epidural anaesthesia with sensory blockade levels as high as T_8-T_{10} inhibits the aldosterone levels during lower limb surgery.

However, reports by Menzies Gow and Cochrane [13] suggest no intraoperative inhibition of hyperaldosteronism in operations of the upper abdomen under combined anaesthesia (generally with the use of halothane plus epidural). The difference in the reported results of the abovementioned studies lies in the fact that the authors have based their analysis on a different type of surgical operation in which they also used halothane. Our results suggest that there is a suppression of the aldosterone reaction during the initial stages of the operation. Thirty minutes after its commencement, we observed a statistically significant difference between the two groups of patients ($p<0.001$). During the subsequent operative stages (60 and 120 minutes), the rise in PA levels was statistically significant ($p<0.001$) for the EA group as well. As a result, we can suggest that the additional epidural block decelerates the appearance of intraoperative hyperaldosteronism, but does not completely inhibit this phenomenon. We believe that factors related to the additional stress imposed on a patient by general anaesthesia contribute to an incomplete cessation of aldosterone reaction due to the epidural block.

References

[1] Sancho I., Re R., Burton J., Haber E.: "The role of the renin-angiotensin-aldosterone system in cardiovascular homeostasis in normal human subjects". *Circulation*, 1976, *53 (3)*, 400.

[2] Gavras H., Hatzinikolau P., Norih W., Bresnahan M., Gavra I.: "Interaction of the sympathetic nervous system with vasopressin and in the maintenance of blood pressure". *Hypertension*, 1982, *3 (3)*, 400.

[3] Houck D., Fiksen-Olsen M., Britton S., Romero C.: "Role of angiotensin and vasopressin on blood pressure of ganglionic blocked dogs". *Am. J. Physiol.*, 1983, *244*, H115, H120.

[4] MacLean M. R., Ungar A.: "Effects of the renin-angiotensin system on the reflex response of the adrenal medulla to hypotension in the dog". *J. Physiol.*, 1986, *373*, 343.

[5] Richards A. M., McDonald D.: "Atrial natriuretic hormone has biological effects in man at physiological plasma concentrations". *J. Clin. Endocrinol.*, 1988, *67*, 1134.

[6] Oelkers W., Kleiners S., Bahr V.: "Effects of incremental infusions of atrial natriuretic factor in andosterone-renin and blood pressure in humans". *Hypertension*, 1988, *12*, 462.

[7] Stell M. K., Gallo R. V., Ganong W. F.: "A possible role for the brain renin-angiotensin in the regulation of LH secretion". *Am. J. Physiol.*, 1983, *245*, 805.

[8] Symonds E. M.: "Renin and reproductions". *Am. J. Obstet. Gynecol.*, 1988, *158*, 754.

[9] Lightman A., Palumbo A., Naftolini F.: "The ovarian renin-angiotensin system". *Seminars in Reprod. Endocrin.*, 1989, *7(1)*, 79.
[10] Stoelting K. R., Miller D. R.: "Basics of Anaesthesia". Second Edition. New York, Churchill Livingstone, 1986, 1086.
[11] Bailey D. R., Miller E. D., Kaplan J. A., Rogers P. W.: "The renin-angiotensin-aldsoterone system during cardiac surgery with morphine-nitrous oxide anaesthesia". *Anaesthesiology*, 1975, *42*, 53.
[12] Brandt M. R., Ugaard K., Kehlet H.: "Epidural analgesia inhibits the renin and aldosterone response to surgery". *Acta Anaesth. Scand.*, 1979, *23*, 267.
[13] Menzies Gow N., Cochrane J. P. S.: "The effect of epidural analgesia on post-operative sodium balance". *Br. J. Surg.*, 1979, *66*, 864.
[14] Oyama T., Taniguchi K., Jin I., Satone S., Kudo T.: "Effects of anaesthesia and surgery on plasma aldosterone concentration and renin activity in man". *Br. J. Anaesth.*, 1979, *51*, 747.
[15] Seitz W., Luebbe N., Bechstein W., Fritz K., Kirchner F.: "A comparison between two types of anaesthesia on the endocrine and metabolic responses to anaesthesia and surgery". *Eur. J. Anesthes.*, 1986, 283.
[16] Oyama T.: "Influence of general anaesthesia and surgical stress on endocrine function". *Contemp. Anesth. Practice*, 1980, *3*, 173.
[17] Kataja J., Viinamaeki O., Punnonen R., Kaukinen S.: "Renin-angiotensin-aldosterone system and plasma vasopressin in surgical patients anaesthetised with halothane or isoflurance". *Eur. J. Anesth.*, 1988, *5 (2)*, 121.
[18] Robertson D., Michelakis A. M.: "Effect of anaesthesia and surgery on plasma renin". *J. Clin. Endocrinol.*, 1972, *34*, 831.
[19] Wernze H., Rietbrock I., Kuhn K.: "Plasma renin activity and plasma aldosterone during anaesthesia and operative stress and b-adrenergic blockade". *Anaesthetist*, 1975, *24*, 471.
[20] Enquist A., Blichert-Toft M., Ugaard K., Brandt M. R., Kehlet H.: "Inhibition of aldosterone response to surgery by saline administration". *Br. J. Surg.*, 1978, *65*, 224.
[21] Hack G.: "Anaesthesie und renin-angiotensin-aldosterone system". *Med. Welt.*, 1983, *34*, 671.
[22] Kidd J. E., Gilchrist N. I., Utley R. J., Nicholls M. G., Vandle L. G.: "Effect of opiate, general anaesthesia and surgery on plasma levels in man". *Clin. Exp. Pharmacol.*, 1987, *14*, 755.

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