

# Stress Hormone Levels in Awake Craniotomy and Craniotomy under General Anesthesia

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## Abstract

To compare stress levels between awake craniotomy and craniotomy under general anesthesia, we analyzed plasma levels of adrenaline, cortisol, adrenocorticotropic hormone (ACTH), noradrenaline and dopamine in a large series of patients. Patients who underwent awake craniotomy in our hospital (n=110) were evaluated at 5 sample times: immediately after arterial line insertion (T1); immediately after head fixation in a head frame (T2); 1 h after start of incision (T3); immediately after relief of head fixation (T4); and immediately after arrival in the intensive care unit (T5). Levels were then compared with those in 15 patients who underwent craniotomy under general anesthesia. Plasma levels of adrenaline were significantly higher during awake craniotomy than in craniotomy under general anesthesia at T1 to T4. Plasma levels of ACTH, cortisol, and noradrenaline in craniotomy were significantly higher under general anesthesia than those in awake craniotomy at T5. No correlations were seen between plasma levels of adrenaline in awake craniotomy and age, sex, preoperative Karnofsky Performance Scale score or postoperative neurological status. In conclusion, plasma levels of adrenaline were significantly higher in awake craniotomy than in craniotomy under general anesthesia during surgery, while plasma levels of cortisol, ACTH and noradrenaline were significantly higher in craniotomy under general anesthesia than those in awake craniotomy just after surgery.

**Keywords:** Adrenocorticotropic hormone; Adrenaline; Awake craniotomy; Cortisol; General anesthesia; Noradrenaline, Stress hormone

## Introduction

Awake craniotomy for brain lesions has recently been reported to offer numerous benefits to patients. Awake craniotomy was initially reported to be associated with improved neurological outcomes in functional areas with maximal removal of lesions compared to results under general anesthesia, thanks to the ability to identify eloquent areas during surgery [1-3]. In addition, awake craniotomy has been reported to minimize both intensive care time and total hospital stay [4,5].

Despite the surgical benefits of awake craniotomy for patients, analysis of the surgical stress associated with awake craniotomy compared with craniotomy under general anesthesia seems likely to be important. Several investigators have reported the responses of inflammatory mediators and amino acids during awake craniotomy [6,7], but no such reports have described stress hormone responses during awake craniotomy. The goal of the present study was to compare stress hormone levels during awake craniotomy with those during craniotomy under general anesthesia.

## Patients and Methods

### Patients

Participants in this retrospective study comprised patients who underwent craniotomy between 2008 and 2013 at Komagome Metropolitan Hospital. A total of consecutive 110 patients with regions suspected preoperatively of containing supratentorial brain tumor underwent awake craniotomy. Another 15 patients with regions suspected preoperatively of containing supratentorial brain tumor underwent craniotomy under general anesthesia. The 110 patients who underwent awake craniotomy comprised 59 men and 51 women, with a median age of 59 years at the time of surgery (range, 25-83 years), while the 15 patients with craniotomy under general anesthesia comprised 7 men and 8 women, with a median age of 63 years at the time of surgery (range, 48-82 years).

Informed consent for craniotomy was obtained from all patients prior to surgery.

### Awake craniotomy

Awake craniotomy was performed as described previously [8]. Briefly, patients were positioned in a supine or lateral position with rigid head fixation (Sugita headrest; Mizuho Medical, Tokyo, Japan) after administration of a local anesthetic (1% xylocaine with epinephrine and 0.75% anapain) at the pin sites and regional field block sites. Under general anesthesia with propofol, dexmedetomidine or remifentanyl, the skin was infiltrated with the same local anesthetic

agent and incised, and neuronavigated craniotomy and incision of the dura was performed.

After suspending administration of the anesthetic agent, oxygen was administered via a mask, and cortical mapping was performed by stimulating the cortex with a modified Ojemann stimulator [9]. To avoid inducing intraoperative seizures, a low-stimulus setting (3-5 mA, 60-Hz biphasic square wave pulse of 1 ms/phase for 4 s) was used. The tumor was removed in the usual fashion. Adequacy of function was continuously assessed during tumor removal [8]. In the language-related area, language functions such as object naming, auditory comprehension, repetition, reading and writing were continuously evaluated. In the motor-related area, motor functions such as tongue movement, eye closing, hand clenching, elbow flexion, knee flexion, and foot flexion were continuously checked. In the sensory-related area, sensory functions such as tactile perception and deep sensation were continuously evaluated. In the non-dominant hemisphere, memory was continuously checked, including forward and backward counting, the frontal assessment battery (FAB) for patients with tumors within the frontal lobes, word and visual memory, and recognition of facial expressions for patients with tumors within the temporal lobes [10]. Tumor removal was assisted by a neuronavigation system (Stealth; Medtronic Sofamor Danek, Osaka, Japan). If neurological deficit occurred at any point during the resection, the operation was interrupted, and neurological function was assessed over the next 5 min. If the neurological deficit did not recover, the operation was terminated. Following completion of tumor resection, intravenous anesthesia was administered using dexmedetomidine or propofol. After closure of the dura, the bone flap was replaced, and the skin was closed in the usual manner.

### Craniotomy under general anesthesia

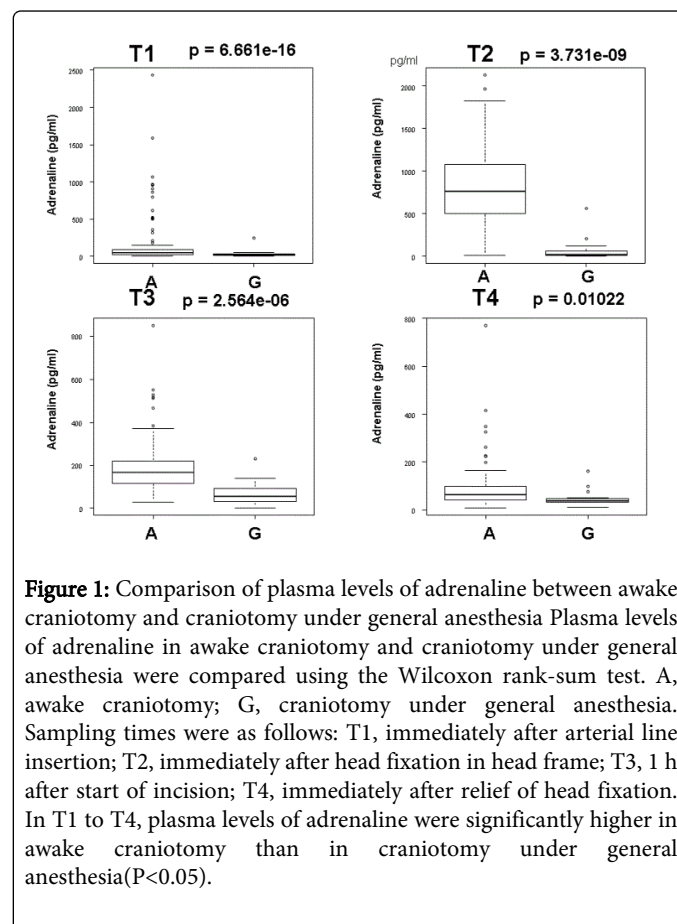
Craniotomy under general anesthesia was performed as follows. Patients were placed in a supine or lateral position with rigid head fixation (Sugita headrest; Mizuho Medical). The skin was incised, and neuronavigated craniotomy and incision of the dura were performed. Anesthesia was maintained with 50% oxygen in air and 3.5% desflurane, remifentanyl at 0.1-0.3 µg/kg/min, propofol at 3-4 mg/kg/h, a fentanyl bolus of 100 µg, and rocuronium at 0.3 - 0.6 mg/kg/h was given as needed. The tumor was removed in the usual fashion. Tumor removal was assisted by a neuronavigation system. Following completion of tumor resection, the dura was closed, the bone flap was replaced, and the skin was closed in the usual manner.

### Sampling during and after craniotomy

Sample times in awake craniotomy and craniotomy under general anesthesia were as follows: T1, immediately after arterial line insertion; T2, immediately after head was fixed by head frame; T3, 1 h after start of incision; T4, immediately after relief of head fixation; and T5, immediately after arrival in the intensive care unit. At each sample time, 4 ml of blood was withdrawn to determine levels of adrenaline, noradrenaline, cortisol, adrenocorticotropic hormone (ACTH) and dopamine. Concentrations of those hormones were analyzed externally by SRL (Tokyo, Japan). Normal ranges of those hormones according to SRL norms were as follows: adrenaline, <100 pg/ml; noradrenaline, 100-450 pg/ml; cortisol, 4-18.3 µg/dl; ACTH, 7.2-63.3 pg/ml; and dopamine, <20 pg/ml.

### Statistical analysis

The Wilcoxon rank-sum test was used to compare stress hormone levels between awake craniotomy and craniotomy under general anesthesia, and mean adrenaline levels at the 5 sample times between men and women and between Karnofsky Performance Scale (KPS) score before surgery 80 (Group A) and <80 (Group B). Correlations between mean adrenaline levels at the 5 sample times and age were analyzed using Spearman's rank correlation. Correlations of mean plasma levels of adrenaline at the 5 sample times among patients showing deterioration, no change or improvement of neurological status after awake craniotomy were analyzed using the Kruskal-Wallis rank-sum test. All p-values were two-sided and values of p<0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University; <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html>); [11], a graphical user interface for R version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R Commander version 1.6-3 that was designed to add statistical functions frequently used in biostatistics.



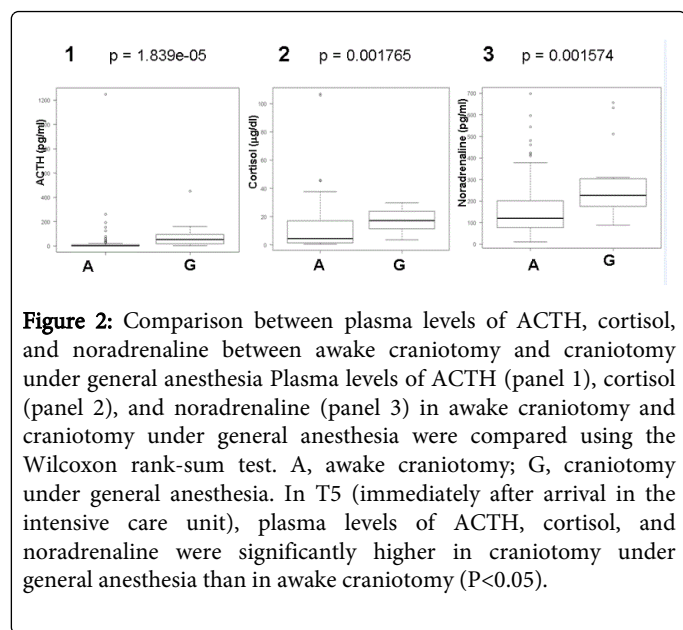
**Figure 1:** Comparison of plasma levels of adrenaline between awake craniotomy and craniotomy under general anesthesia. Plasma levels of adrenaline in awake craniotomy and craniotomy under general anesthesia were compared using the Wilcoxon rank-sum test. A, awake craniotomy; G, craniotomy under general anesthesia. Sampling times were as follows: T1, immediately after arterial line insertion; T2, immediately after head fixation in head frame; T3, 1 h after start of incision; T4, immediately after relief of head fixation. In T1 to T4, plasma levels of adrenaline were significantly higher in awake craniotomy than in craniotomy under general anesthesia (P<0.05).

### Results

Plasma levels of adrenaline were significantly higher in awake craniotomy than in craniotomy under general anesthesia at T1-T4 according to the Wilcoxon rank-sum test (p<0.05) (Figure 1, Table 1). On the other hand, no difference in plasma levels of adrenaline was

seen between awake craniotomy and craniotomy under general anesthesia at T5 (Table 1).

Plasma levels of ACTH, cortisol, and noradrenaline were significantly higher for craniotomy under general anesthesia than for awake craniotomy at T5 using the Wilcoxon rank-sum test ( $P < 0.05$ ) (Figure 2, Table 1). Conversely, no significant differences in plasma levels of ACTH, cortisol, or noradrenaline were seen between awake craniotomy and craniotomy under general anesthesia at T1-T4 (Table 1). No significant difference in plasma levels of dopamine was seen between awake craniotomy and craniotomy under general anesthesia at any time points using the Wilcoxon rank-sum test (Table 1).



**Figure 2:** Comparison between plasma levels of ACTH, cortisol, and noradrenaline between awake craniotomy and craniotomy under general anesthesia. Plasma levels of ACTH (panel 1), cortisol (panel 2), and noradrenaline (panel 3) in awake craniotomy and craniotomy under general anesthesia were compared using the Wilcoxon rank-sum test. A, awake craniotomy; G, craniotomy under general anesthesia. In T5 (immediately after arrival in the intensive care unit), plasma levels of ACTH, cortisol, and noradrenaline were significantly higher in craniotomy under general anesthesia than in awake craniotomy ( $P < 0.05$ ).

Noradrenaline1	179 ± 110	198 ± 89
Noradrenaline2	172 ± 130	210 ± 116
Noradrenaline3	160 ± 130	447 ± 1168
Noradrenaline4	168 ± 151	175 ± 103
Noradrenaline5#	162 ± 131	282 ± 179
Dopamine1	7 ± 5	9 ± 6
Dopamine2	8 ± 6	10 ± 6
Dopamine3	8 ± 6	8 ± 7
Dopamine4	9 ± 7	8 ± 5
Dopamine5	8 ± 7	10 ± 8

**Table 1:** Comparison of stress hormone levels between awake craniotomy and craniotomy under general anesthesia; Units for adrenaline, ACTH, noradrenaline, and dopamine were picograms/milliliter; units for cortisol were micrograms/deciliter. 1=T1, 2=T2, 3=T3, 4=T4, 5=T5; # Indicates that the level of stress hormone was significantly different ( $p < 0.05$ ).

No correlation was identified between mean plasma levels of adrenaline at the 5 sample times under awake craniotomy and age using Spearman's rank correlation (Figure 1-3). No significant correlations were identified between mean plasma levels of adrenaline at the 5 sample times and either sex or preoperative KPS score using the Wilcoxon rank-sum test (Figure 2 and 3). No correlation was seen between mean plasma level of adrenaline at the 5 sample times and neurological status after surgery using Spearman's rank correlation (Figure 3).

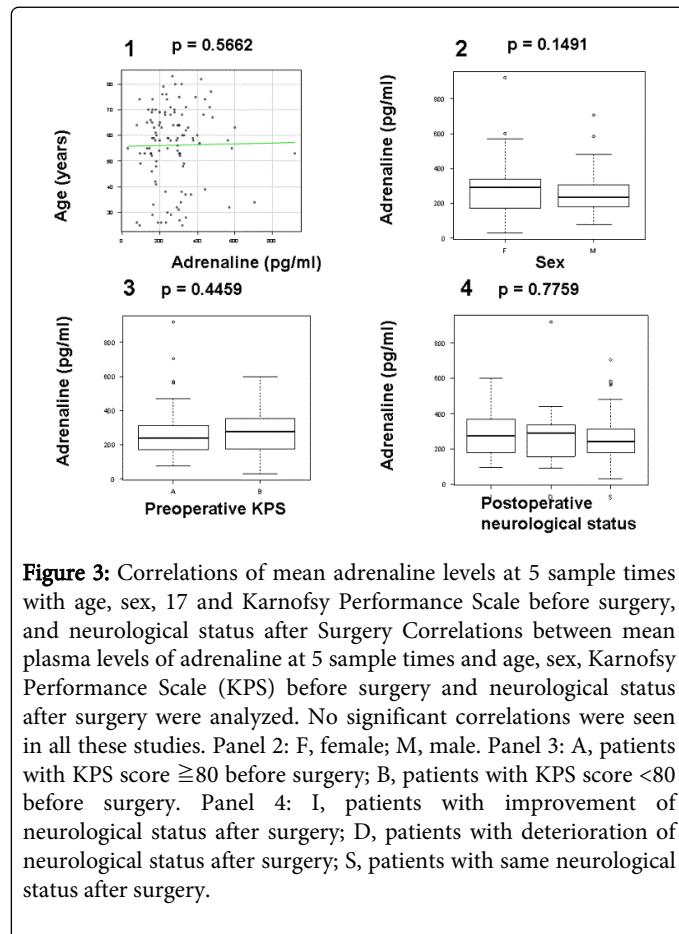
## Discussion

This study found that plasma levels of adrenaline were significantly higher during awake craniotomy than during craniotomy under general anesthesia. The increased levels of adrenaline during awake craniotomy might agree with the increased heart rate and systolic arterial blood pressure seen during awake craniotomy [12]. On the other hand, plasma levels of ACTH, cortisol and noradrenaline were significantly higher with craniotomy under general anesthesia than with awake craniotomy on arrival at the intensive care unit after surgery. Tacconi et al. [13] reported a similar result with postoperative cortisol levels lower in a group with awake video-assisted thoracoscopic surgery compared with a group under general anesthesia.

Several studies have reported patient perceptions of stress during awake craniotomy. According to a questionnaire assessing aspects of patient perceptions of the procedure, most patients tolerate awake craniotomy well [14]. Eighty-seven percent of patients reported feeling at ease during awake craniotomy, indicating high levels of patient satisfaction [15]. Scores for postoperative pain and physical disorders were likewise significantly lower in awake craniotomy than in craniotomy under general anesthesia [16]. On the other hand, awake surgery has led to postoperative psychological sequelae resembling posttraumatic stress disorder in some cases [17]. Although awake craniotomy is useful to preserve neurological function after surgery compared to craniotomy under general anesthesia, the risk of stress during awake surgery should be considered, because adrenaline levels

Stress hormones	Awake	General anesthesia
Adrenaline 1#	170 ± 353	33 ± 61
Adrenaline 2#	822 ± 416	74 ± 147
Adrenaline 3#	194 ± 124	68 ± 58
Adrenaline 4	88 ± 93	51 ± 38
Adrenaline 5	82 ± 97	121 ± 117
ACTH1	21 ± 25	14 ± 9
ACTH2	18 ± 40	11 ± 7
ACTH3	36 ± 73	25 ± 78
ACTH4	24 ± 123	5 ± 8
ACTH5#	25 ± 124	84 ± 113
Cortisol1	11 ± 8	11 ± 4
Cortisol2	10 ± 9	9 ± 3
Cortisol3	16 ± 43	8 ± 4
Cortisol4	11 ± 20	4 ± 4
Cortisol5#	11 ± 17	18 ± 9

were significantly increased during awake surgery compared to craniotomy under general anesthesia. However, increased levels of postoperative stress hormones after craniotomy under general anesthesia might be related to the high scores for postoperative pain and physical disorders seen using this method.



Why were adrenaline levels increased during awake craniotomy, while ACTH, cortisol and noradrenaline levels increased after craniotomy under general anesthesia? Several investigators have reported a dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system. In Alzheimer's disease and major depression, dissociation is seen between both systems [18,19]. Moreover, different responses to stress are exhibited by the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system. The hypothalamus-pituitary-adrenal axis quickly habituates, while the sympathetic nervous system shows rather uniform activation patterns with repeated stress [20]. Since patients with brain tumors may well have experienced repeated episodes of stress, some degree of habituation might exist in the hypothalamus-pituitary-adrenal axis of patients undergoing awake craniotomy. On the other hand, stress levels of patients might be much higher just after craniotomy under general anesthesia than during awake craniotomy [6]. In addition, the differences in anesthetic drugs used between awake surgery and general anesthesia might also have contributed to the differences between systems. Further investigation is required to analyze discrepancies in the reactions of both systems.

As for biological markers of stress during awake craniotomy, Klimek et al. reported the inflammatory profiles of patients treated

under awake craniotomy and craniotomy under general anesthesia to evaluate differences in surgical stress between groups, because surgical stress triggers inflammatory responses and releases mediators such as interleukins into human plasma [7]. They concluded that awake craniotomy does not cause any inflammatory response significantly different from that caused by craniotomy under general anesthesia. Moreover, they claimed that the visual analogue scale pain score was significantly lower in the awake group compared to the general anesthesia group at 12 h postoperatively. Similarly, Hol et al. (2009)[6] reported that awake craniotomy is likely to be physically and emotionally less stressful than general anesthesia after analyzing amino acid profiles to gain insights into physical and emotional stress.

Is the increase in adrenaline during awake craniotomy correlated to bad reactions of the brain or body induced by stress? Plasma levels of adrenaline did not correlate with neurological function, in terms of improvement, no change or deterioration after surgery in our study (Figure 3). This may be at least partly due to the blood-brain-barrier, which is impermeable to circulating adrenaline thanks to the protective influence of the locus ceruleus [21]. Moreover, vagal sensory fibers, directly activated by plasma adrenaline, represent the afferent limb of a negative feedback loop that adjusts the activity of the sympathoadrenal system [22]. Actually, in our study, increased plasma levels of adrenaline at T2 (fixation of head) had decreased rapidly by T3 (1 h after incision of the skin), a change that might be induced by negative feedback (Table 1).

In conclusion, plasma levels of adrenaline were significantly higher in awake craniotomy than in craniotomy under general anesthesia during surgery, while plasma levels of cortisol, ACTH and noradrenaline were significantly higher in craniotomy under general anesthesia than in awake craniotomy just after surgery.

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