

# Stress and fluid restriction before anesthesia induction, investigation of the effects of the patient's clinic, endocrine responses, and the level of the Nesfatin-1

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## Ethics Committee Approval

Firat University Faculty of Medicine Clinical Research Ethics Committee (01.11.2012 / 18-02)

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## Conflict of Interest

No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Preoperative fasting, fluid restriction and stress trigger many hormonal responses, one of which is the newly described Nefatin-1. It has important effects on energy metabolism and stress. In this study, we aimed to examine the relationship between stress, fasting, fluid restriction, and Nesfatin-1.

**Methods:** A total of 100 ASA I-II adult patients between 18 and 60 years of age with no psychiatric, cardiovascular, or metabolic disorders, who were operated under general anesthesia for various reasons at Firat University Hospital between June and November 2013 were included in this randomized prospective case-control study. Patients were categorized into fluid restriction (Group 1) and no-fluid restriction (Group 2) groups. These groups were further sub-categorized as those receiving (Groups 1A and 2A) and not receiving pre-medication (Group 1B and Group 2B). State Trait Anxiety Inventory was applied to all patients by an independent member of the research team before the surgical procedure. Also, blood samples were obtained 6-8 hours, 1 hour, and just before the induction to measure insulin, glucose, epinephrine, norepinephrine, cortisol, and Nesfatin-1 levels.

**Results:** In both groups, the test score for pre-operative anxiety was 44. While there were no differences in serum insulin levels between the study groups ( $P>0.05$ ), serum glucose and epinephrine levels were higher in Group 1A than in other groups ( $P<0.05$  for both). Except for the 2<sup>nd</sup> period, serum norepinephrine levels were elevated in all stages ( $P<0.05$ ). Serum cortisol levels were higher in Group 2B ( $P<0.05$ ), while serum Nesfatin-1 levels were higher in Group 2A ( $P<0.05$ ).

**Conclusion:** According to our findings, the highest reflection of stress in patients, together with clinical and endocrine responses, coincided just before the induction period. Further studies are warranted before firmer conclusions can be drawn regarding the association between Nesfatin-1 and anxiety. We believe that if the pathophysiological mechanisms between anxiety and Nesfatin-1 are clarified, Nesfatin-1 targeting treatment approaches can be tried in the clinic.

**Keywords:** Surgery, Premedication, Fluid restriction, Anxiety, Nesfatin-1

## Introduction

Preoperative fasting and fluid restriction used in elective surgeries is a routine anesthetic preparation that reduces the risk of aspiration. However, this process can put the patient in distress both metabolically, physiologically, and psychologically [1]. Hunger, fluid restriction and emotional stress caused by surgery affect the pituitary hormones. Catabolic hormones such as cortisol, glucagon and catecholamines increase, while anabolic hormones such as insulin and testosterone are inhibited [2]. However, it is also known that emotional stress causes the release of adrenaline and noradrenaline from the suprarenal medulla [3].

Nesfatin-1 is a recently described saturation molecule in the hypothalamus and has multiple endocrine functions [4,5]. Nesfatin-1 has an autonomous and endocrine effect on energy expenditure and affects eating [6,7]. It also plays a role in the regulation of emotional and behavioral situations. In experimental animal models, Nesfatin-1 was activated in the rat brain in psychological stress [8]. Plasma Nesfatin-1 level was higher in patients with high anxiety compared to those with low anxiety. A significantly high correlation was found between plasma Nesfatin-1 level, total stress score and depression score [9]. We used the State-Trait Anxiety Inventory (STAI) test, which is the standard test for the measurement of anxiety in patients.

This study aimed to investigate the effects of stress and fluid restriction before anesthesia induction on the patients' clinical status, endocrine responses and the level of a new peptide-made hormone, Nesfatin-1.

## Materials and methods

Previous studies were referenced for sample size. There were 100 patients, 25 patients in each group, with a minimum sample size at 0.05 alpha error and 0.8 beta error. Permission was obtained from Firat University Faculty of Medicine Clinical Research Ethics Committee (01.11.2012 / 18-02). One hundred ASA 1-2 patients between the ages of 18-75 years who were operated between June-November 2013 at Firat University Hospital were included in this randomized prospective case-control study. Patients with psychiatric, cardiovascular, and metabolic disorders were excluded.

The patients were randomly divided into two groups, as those with and without fluid restriction. Both groups were also randomly divided into 2 subgroups, as those who did and did not receive premedication. Randomization was provided by a closed envelope method by a blinded operating room staff who did not participate in the study.

Group 1 (n=50): These patients fasted and fluid-restricted preoperatively for 4-6 hours before induction.

Group 1A (n=25): These patients received premedication. Intramuscular (IM) midazolam (0.07 mg/kg) and intravenous (IV) atropine sulfate (0.01 mg/kg) were administered.

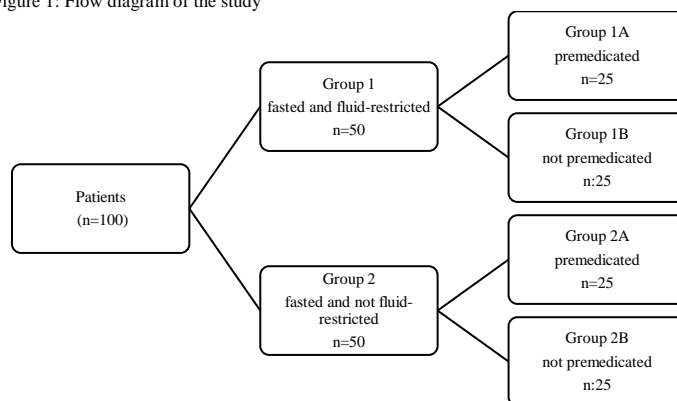
Group 1B (n=25): These patients did not receive any premedication.

Group 2 (n=50): These patients who fasted preoperatively did not restrict fluids until 1 hour before the induction of anesthesia.

Group 2A (n=25): These patients received premedication. IM midazolam (0.07 mg/kg) and IV atropine sulfate (0.01 mg/kg) were administered.

Group 2B (n=25): These patients did not receive premedication.

Figure 1: Flow diagram of the study



Demographic data of the patients were recorded. All patients received the (STAI) State-Trait Anxiety Inventory test which shows state and continuous anxiety before the operation (STAI 1, STAI 2). Systolic blood pressures (SAP), diastolic blood pressures (DAP) and heart rates were measured and recorded for 6 hours before the induction (period 1), 1 hour before induction (period 2) and immediately before induction (period 3). Within the same periods, Nesfatin-1, epinephrine, norepinephrine, glucose, insulin, and cortisol values were measured and recorded.

### Statistical analysis

SPSS 12.0 (The Statistical Package for the Social Sciences, Chicago, USA) program was used for statistical analyses. The data were recorded as mean (SD). Variation analysis (ANOVA) was used in the analysis of parametric tests, and a post-Tukey HSD test was used when a significant difference was found in comparison between the groups. Paired t-test was used to compare repetitive measurements within the group. The relationship between patients' Nesfatin-1 levels and mood and anxiety disorders was evaluated with the Pearson correlation test. *P*-value <0.05 was considered significant.

## Results

### Demographic and hemodynamic data

Thirty-three percent (n=33) of the patients in the study were females. The mean age of Groups 1A, 1B, 2A and 2B were 30.16 (10.78) years, 32.84 (12.12) years, 26.48 (5.59) years, and 27.72 (7.80) years, respectively. The demographic data of the patients were similar between the groups (*P*>0.05) (Table1).

Table 1: Demographic data of patients

	Group 1		Group 2	
	Group 1A (n=25)	Group 1B (n=25)	Group 2A (n=25)	Group 2B (n=25)
Gender (M/F)	17/8	16/9	17/8	17/8
Age (year)	30.16 (10.78)	32.84 (12.12)	26.48 (5.59)	27.72 (7.80)
Weight (kg)	73.32 (9.24)	67.80(7.83)	70.36 (6.89)	73 (9.26)

The SAP, DAP and heart rate values did not differ among the groups (*P*>0.05). However, SAP values were significantly higher in all groups in the 3rd period compared to the 1st period (*P*<0.05). DAP values in the 2nd period were significantly higher in all groups compared to the 1st period (*P*<0.05). The heart rate values in period 2 were significantly

higher compared to period 1 ( $P<0.05$ ). Time-dependent changes within the groups are given in Table 2.

Table 2: Hemodynamic changes in patients

	Period	Group 1		Group 2	
		Group 1A (n=25)	Group 1B (n=25)	Group 2A (n=25)	Group 2B (n=25)
Systolic blood pressure (mmHg)	1	113.96 (12.10)*	112 (11.18)*	107.80 (10.51)*	111.60(7.46)*
	2	118.84 (13.67)	114.00 (8.03) <sup>φ</sup>	111.40 (9.41) <sup>φ</sup>	113.80 (10.82) <sup>φ</sup>
	3	125.56 (11.80)	124.24 (8.83)	128.04 (13.22)	125.00 (8.83)
Diastolic blood pressure (mmHg)	1	69.36 (7.17)	68.20 (9.00)	68.20 (8.88) <sup>κ</sup>	71.00 (7.50)
	2	72.76 (10.74)	71.00 (8.03)	73.00 (7.77)	72.20 (6.62)
	3	76.28 (8.65)	76.32 (8.57)	77.60 (10.17)	75.88 (6.85)
Heart rate (Pulse / min)	1	79.64 (9.30)	76.36 (9.18)	73.04 (5.70) <sup>κ</sup>	74.52 (7.26) <sup>κ</sup>
	2	79.04 (13.47)	77.72 (7.19)	76.16 (6.23)	78.48 (9.06)
	3	79.52 (10.13)	75.24 (13.89)	78.16 (10.12)	77.92 (11.60)

Period 1: 6 hours before induction, Period 2: 1 hour before induction, Period 3: Just before induction. \*  $P<0.05$  Between Period 1 and Period 3. & Between Period 1 and Period 2. <sup>φ</sup>  $P<0.05$  Between Period 2 and Period 3.

**Biochemical parameters**

Serum glucose values of group 1A significantly differed from the other groups in the 2nd period ( $P<0.05$ ). Serum glucose values were significantly higher in Group 1A (81.68 (29.55)) compared to Group 2A (62.76 (27.14)), in group 1B (82.12 (17.87)) compared to group 2A, and in group 2B (84.32 (17.08)) compared to group 2A ( $P<0.05$ ).

Insulin values were similar between the two groups ( $P>0.05$ ; however, those of Group 2A were significantly higher in the 2nd period (4.68 (2.62)) compared to the first period (3.88 (2.70)). Cortisol level in group 2B was significantly higher than group 2A ( $P<0.05$ ).

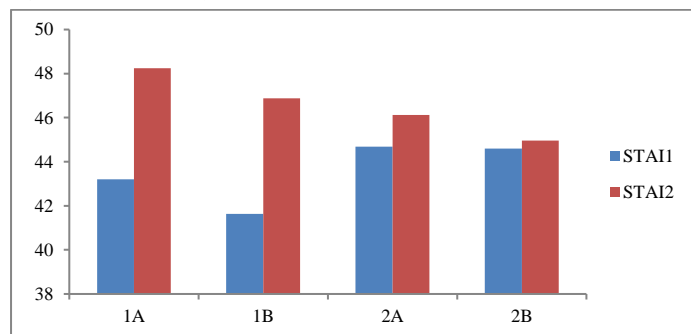
Epinephrine values in the 1st period were significantly higher in group 1A (70.67 (17.90)) compared to other groups ( $P<0.05$ ). Likewise, epinephrine values in the 2. period were higher in group 1A (57.76 (18.42)) than group 1B (46.21 (8.98)) and group 2A (43.98 (6.60)), in group 2B (56.20 (11.22)) than group 1B and 2A ( $P<0.05$ ). Epinephrine values in the 3rd period were significantly higher in group 1A (76.79 (16.61)) compared to all other groups ( $P<0.05$ ) and in group 1B (54.14 (8.12)) compared to Group 2A (42.14 (6.69)) ( $P<0.05$ ). In the intergroup evaluation, while the norepinephrine value in group 1A was significantly higher in all periods ( $P<0.05$ ), that in group 1B (430.36 (147.21)) was significantly higher in the 1st and 2nd periods compared to Groups 2A (172.40 (38.33)) and 2B (133.44 (30.15)) ( $P<0.05$ ). In addition, in the 3rd period, norepinephrine levels were significantly lower in group 1B (307.92 (97.28)) compared to group 1A (753.48 (188.72)) and in group 2A (198.32 (55.90)) compared to group 2B (361.64 (165.63)) ( $P<0.05$ ).

Serum Nesfatin-1 levels of group 2A was significantly higher than group 2B in inter-group evaluation ( $P<0.05$ ). In intra-group evaluation, the level of Nesfatin1 in group 2A (21.08 (6.20)) was significantly higher in the 2nd period and that in group 1A was significantly higher in the 2nd period (15.24 (6.11)) compared to the 3rd period (17.78 (7.86)) ( $P<0.05$ ). According to the results of statistical analysis between all groups, changes in patients' biochemical parameters are summarized in Table 3.

**STAI Test (State and Trait Anxiety Scale) analysis**

The mean anxiety score was 44. Although there were no significant differences in STAI-1 between the groups, it was highest in group 2A (44.68) and lowest in group 1B (41.64) ( $P>0.05$ ). Although STAI-2 scores were similar, it was highest in group 1A (48.24), and lowest in group 2B (44.96) ( $P>0.05$ ) (Figure 2).

Figure 2: STAI Test Analysis



**Discussion**

The patient, who is informed about the need for an operation, faces a stressful situation. This anxiety reaches the maximum level especially in the preoperative preparation room. The main reason for this anxiety is pain and fear of not waking up after surgery [10-12]. Detailed information and premedication prior to the operation have an important role in the prevention of this preoperative incapability [9, 13]. This anxiety, pre-operative fasting, and fluid restriction significantly increase the level of stress. It induces various physiological, metabolic, and psychological responses to protect the body from this stress [3, 14]. The body's response is characterized by increased activation of catabolic and immunosuppressive hormones from the pituitary gland with activation of the sympathetic nervous system [15]. The aim of this study is to investigate the effects of stress and fluid restriction before anesthesia induction on patient clinic, endocrine responses, and a new peptide-made hormone, Nesfatin-1 level. The State-Continuity Anxiety Scale (STAI 1-STAI 2) is an easy-to-apply scale that can be answered by the individual as well as the patient's hemodynamic and biochemical data in the measurement of anxiety. Taşdemir et al. [16] showed that preoperative anxiety was significantly higher than postoperative anxiety. Domar et al. [17] found an average score of 45 preoperatively. In our study, according to the results of the statistical analysis for the STAI test, no significant differences were observed between the groups. The preoperative anxiety score in our study was 44 on average. This is similar to the results of other studies.

In our study, systolic and diastolic blood pressure values increased significantly just before induction in all groups. Although there were no statistically significant differences in the heart rate values between the groups, the intra-group evaluation increased significantly 1 hour before induction. This indicates that the anxiety caused by surgery increases as the time of operation approaches and premedication is not effective enough to prevent this.

The pituitary hormones secreted in response to stress and increased sympathetic activity cause the body to transition to a new state both hemodynamically and metabolically. Therefore, heart minute volume and tissue perfusion are increased, and body temperature rises. Blood glucose is increased with the increase of catabolic hormones such as cortisol, adrenaline, and insulin, in addition to glycolysis, gluconeogenesis, and lipolysis. The serum insulin levels in our study were similar in inter- and intra-group evaluations. Serum glucose levels of group 1A (fasted, fluid restricted and premedicated group) also showed a significant change compared to other groups. The high glucose levels of

group 1A may be due to the anxiety caused by fluid restriction. Catecholamines have important physiological effects in response to stress. They activate glycogenolysis, gluconeogenesis, lipolysis and ketogenesis in the liver. This is because they lower insulin and increase glucagon [18-20]. They also increase blood pressure and heart rate [21]. There are many stimuli that lead to catecholamine release, such as hypovolemia, hypoglycemia, hypoxemia, pain and fear. Hypovolemia is best correlated with catecholamine release [22]. In our research, epinephrine and norepinephrine levels were higher in group 1A compared to the other groups. These results support our view that hunger and fluid restriction increase the stress level. It is known that surgical stimulation, anesthesia, psychic, and emotional stress increase cortisol release [23]. Cortisol potentiates the effects of epinephrine and glucagon, causing hyperglycemia. It also activates gluconeogenesis, proteolysis, and lipolysis. As a result of all these processes, blood glucose rises and tries to supply the vital organs with the necessary energy.

Nesfatin-1 is a recently described molecule. Studies show that besides the central nervous system, it is secreted from the pancreas, adipose tissue, and gastric mucosa [7, 24-26]. It has been shown in human milk [27]. Food and water intake has been shown to increase Nesfatin-1 levels [7, 24, 28]. Stengel et al. [29] found low levels of Nesfatin-1 in rats that were fasted for 24 hours. Tsuchiya et al. [30] stated that there is a negative correlation between Nesfatin-1 and BMI. The increase of Nesfatin-1 secretes glucose-stimulated insulin from pancreatic beta cells [31, 32]. Foo et al. [7] showed that Nesfatin-1 administration decreases blood glucose level of hyperglycemic rats (type 2 DM) depending on the dose and time. Nesfatin-1 is also effective in the regulation of emotional and behavioral states. In experimental animal models, Nesfatin-1 activation in the rat brain increased psychological stress [8]. In their study, Hofmann et al. [33] found that plasma Nesfatin-1 level was higher in the group of high anxiety compared to patients with low anxiety. There was a statistically significant correlation between plasma Nesfatin-1 level, total stress score and depression score. Günay et al. [34] reported that Nesfatin-1 level was low in their study on normal weight men with general anxiety. In our study, the nesfatin-1 levels of only group 2A was significantly higher than group 2B. In the intra-group evaluation, Nesfatin1 level in group 2A was high in the second period.

The level of Nesfatin1 in Group1A was significantly higher in the 3rd period than in the 2nd period. Also, group 2A had the lowest glucose levels in comparison to other groups. This can be regarded as an indicator of the antihyperglycemic effect of Nesfatin-1. Based on our results, anxiety score was compatible in the STAI 1 test, but no correlation was observed in the STAI-2 test. We think this may be related to glucose level.

The limitations of this study are as follows: The study was performed only in operations involving general anesthesia. Therefore, the data were more limited as it did not include patients with regional anesthesia. In addition, it should be kept in mind that anxiety analyses are affected by the sociodemographic statuses of the patients.

### Conclusion

According to our findings, the highest reflection of stress in patients seems to coincide with the clinical and

endocrine responses just before the induction period. Preoperative fluid replacement and premedication maintain hemodynamic stability and contribute positively to energy balance by increasing the level of Nesfatin-1. If the pathophysiological mechanisms are clarified, we think that Nesfatin-1 can be used in the treatment of diseases affecting energy metabolisms such as diabetes and obesity, and in reducing perioperative complications.

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