

## Sedation impact over perioperative endocrine stress response in patients with increased anxiety undergoing total arthroplasty of the inferior limb

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**ABSTRACT.** Purpose. Decreasing anxiety level through intraoperative sedation and postoperative anxiolysis can modulate perioperative neuroendocrine stress response. Material and Methods. This randomized prospective clinical study includes 48 patients subjected to total articular endoprosthesis at hip and knee level, respectively. The patients included in the study were equally divided into 2 groups, each group comprising 24 patients: 12 patients with knee prosthesis (TKA), and 12 patients with hip prosthesis (THR). All patients benefited from subarachnoid anaesthesia. In order to evaluate anxiety, there was used a STAI-X2 questionnaire for determining preoperative anxiety and STAI-X1 questionnaire for determining preoperative, post-operative anxiety, immediately and the following day. The numerical scale was used to evaluate preoperative pain (NRS), while the Wilson scale was used for quantifying the intraoperative sedation. Results. The situation anxiety in group As decreases significantly immediately after surgery, ( $p < 0.0001$  for TKA, THR respectively), the following day after surgery patients show slightly increased scores ( $p = 0.0002$  for TKA,  $p = 0.0004$  for THR) in comparison to the end of surgery. In the sedated patients (Group As), both for TKA and for THR, the level of cortisolemia significantly decreases immediately after surgery ( $p < 0.0001$  for TKA, THR, respectively). Seric glycemia is maintained relatively stable (even decreasing in the case of THR ( $p = 0.00014$ ) immediately after surgery in the patients in group As. Conclusions. Immediately after surgery, faced with surgery, there is a significant correlation: situation anxiety-cortisolemia-glycemia. Intraoperative sedation and postoperative anxiolysis in patients with high anxiety may indirectly modulate the postoperative neuroendocrine response.

**KEYWORDS:** anxiety, stress response, arthroplasty

### Introduction.

Acute stress during the post-operative period has four major sources: tissular injury, pain, anxiety, a possible neurotoxicity of anaesthetical agents. One, or all of these factors, may detrimentally act at brain level, with known major effects on certain areas, like the hippocampus and the hypothalamic-pituitary-adrenal axis (1).

Stress hormones negatively affect various systems, including the brain (2), through high levels of glucocorticoids, or their prolonged release, or an inadequate defensive as a protective response to stress factors. The alterations induced by the stress in the GABA-serotonergic system contribute to the derangement of the hypothalamic-pituitary-adrenal axis and even to the development of certain psychiatric disorders (depression) in sensitive individuals (3).

There are several studies reporting that preoperative anxiety contributes to further brain alterations. Sometimes, patients undergo high levels of an acute psychological stress during the perioperative period (4), prolonging over weeks or months before the surgery itself. A majority of the proposed patients for total endoprosthesis in the inferior limb can be classified in this category. They are patients with a permanent chronic illness, often considering themselves as socially undesired due to their limited mobility. The control of perioperative stress factors may diminish, and even discharge, undesired post-operative serious consequences. For example, modulating the perioperative anxiety seems to be beneficial (5).

Anxiolysis and sedation are often used by anaesthetists, although during a recent French investigation only 36% of these frequently used sedation along regional anaesthesia in TKA (6). There are certain studies supporting the idea that

indications for sedation should be restricted to the elderly (7).

### Material and Methods.

This randomized prospective clinical study includes 48 patients out of a number of 154 patients subjected to total articular endoprosthesis at hip and knee level, respectively. In this study the inclusion criteria were: patients over 55 years old, diagnosed with primary osteoarthritis, who gave their assent for the study and were preoperatorily evaluated with an anxiety (X2) level higher than 42 (the average recommended by the interpretation of STAI questionnaire for the Romanian population) and presented a high and very high level of situational anxiety (STAI X1>50).

The compulsory exclusion criteria were: endocrine diseases, diabetes mellitus, surgeries under the age of 6 months; diagnosed psychiatric disorders, under treatment; history or recent use of medicines that affects the sympathetic-adrenergic response or the hormone secretion (corticosteroids, adrenergic beta blockers); intraoperative complications of surgical technique prolonging the operatory time; patients requiring intraoperative transfusions over 2 units of CE.

The patients included in the study were equally divided into 2 groups: As and B, each group comprising 24 patients: 12 patients with knee prosthesis (TKA), and 12 patients with hip prosthesis (THR). In all patients there was performed a total cemented arthroplasty, using the same surgical technique, according to the prosthesis type (THR, TKA, respectively). All the surgical interventions were performed between 9 and 11 A.M., keeping the circadian dynamics of cortisol. The open, friendly behaviour were comparable in all patients.

The intraoperative monitoring was performed after ASA standards: pulse, non-invasive AP, pulse oximetry. The quantification of blood losses in the vacuum was closely monitored. No patient received any medication. All patients benefited from subarachnoid anaesthesia with 3 ml bupivacain, 0,5% isobar, being added 20 µg Fentanyl. The sensitive and motor block was complete. Patients in group A underwent an intraoperative and intravenous sedation with: Propofol (10-40 µg/Kg/min), and Dormicum (3 mg initially, then 1 mg repeatedly, in order to keep the sedation level of patients at ≤3); postoperatory, these patients received Diazepam: 0,1 mg/kg. Patients in group B received a placebo medication.

In order to evaluate anxiety, there was used a STAI-X2 questionnaire for determining preoperatory anxiety and STAI-X1 questionnaire for determining preoperatory, post-operatory anxiety, immediately and the following day, before mobilization. The numerical scale was used to evaluate preoperatory pain (NRS), while the Willson scale was altered for quantifying the intraoperatory.

Variables of endocrine stress: glycemia, seric cortisol, insulin were measured preoperatorily, in the morning of the surgery, immediately and the following day after surgery.

### Results.

24/48 hours preoperatory evaluation of patients included in the study according to diagnosis (coxarthrosis/gonarthrosis) (Table 1).

**Table 1. Preoperatory evaluation of patients included in the study according to diagnosis (coxarthrosis/gonarthrosis)**

	Coxarthrosis (n=24)	Gonarthrosis (n=24)
Age (years)	68,58±7,08	68,41±5,17
Sex (F/M)	17/7	18/6
Environment (C/V)	10/14	10/14
Education (P/S/H/U)	1/18/5/0	4/17/3/0
Family Support (Y/N)	21/3	19/5
Chronic Pain (years)	2,47±0,77	3,25±0,70
Preoperatory Pain (NRS)	6,45±1,03	6,66±1,31
STAI - X2	52,79±2,67	57,5±4,56
Haemoglobin (g/dl)	12,97±1,47	13,55±1,48
Haematocrit (%)	38,10±4,74	39,58±3,52

From the preoperatory test there can be seen that, according to the demographic data, the groups are approximately homogenous.

Immediately after surgery (day 0), situational anxiety (STAI X1) and endocrine variables evaluation, according to diagnosis (Table 2).

**Table 2. Situational anxiety (STAI X1) and endocrine variables evaluation, immediately after surgery, according to diagnosis**

Variables	As		B	
	PTG	PTC	PTG	PTC
STAI X2	55,66±3,51	53,25±2,31	59,33±4,74	52,33±2,92
STAI X1	60,91±4,05	56,5±3,47	62,08±4,53	57,33±2,77
G0	123,08±24,04	119,83±14,65	121,58±21,58	116,33±14,26
Co0	605,76±70,6	547,02±84,87	590,62±54,47	537,21±58,39
I0	10,17±4,26	11,06±3,86	9,76±2,76	10,61±3,59

Immediately after surgery (day 0), situational anxiety and endocrine variables evaluation, in study groups (As and B) (Table 3).

**Table 3. Situational anxiety and endocrine variables evaluation, immediately after surgery in study groups (As and B).**

Variables	As		B	
	PTG	PTC	PTG	PTC
STAI X2	55,66±3,51	53,25±2,31	59,33±4,74	52,33±2,92
STAI X1	60,91±4,05	56,5±3,47	62,08±4,53	57,33±2,77
G0	123,08±24,04	119,83±14,65	121,58±21,58	116,33±14,26
Co0	605,76±70,6	547,02±84,87	590,62±54,47	537,21±58,39
IO	10,17±4,26	11,06±3,86	9,76±2,76	10,61±3,59

There can be seen a high average score of glycemia and cortisolemia over the laboratory maximum threshold value for these variables, a reference threshold value in this study.

Statistical Correlation Between the Preoperative Level of Situation Anxiety (X1), Glycemia (G0), Cortisolemia (Co0) and Insulinemia (IO), in Patients Proposed for TKA (Table 4).

**Table 4. Preoperative correlation: situation anxiety – endocrine variables in patients with gonarthrosis**

	X1	G0	Co0	IO
X1	1			
G0	0.832	1		
Co0	0.883	0.730	1	
IO	-0.172	-0.265	-0.250	1

We noticed an important direct correlation (r=0,88): situation anxiety – cortisolemia immediately after surgery. A similar correlation may also be seen between the level of anxiety and glycemia (r=0,83); the latter is correlated to the level of cortisolemia (r=0,73).

In patients with coxarthrosis there may also be seen a high average score over the reference threshold of glycemia and cortisolemia, but at a lower rate.

Statistical Correlation Between the Preoperative Level of Situation Anxiety, Glycemia, Cortisol and Insulin in Patients Undergoing THR (Table 5).

**Table 5. Preoperative correlation: situation anxiety – endocrine variables in patients with coxarthrosis**

	X1	G0	Co0	IO
X1	1			
G0	0.762	1		
Co0	0.872	0.744	1	
IO	-0.599	-0.797	-0.567	1

Before surgery, there may be seen an important direct correlation (r=0,87), similar

to that seen in the patients proposed for TKA, between the level of cortisolemia and situation anxiety. Satisfactory correlations may be seen between the level of glycemia and the level of situation anxiety (r=0,76), and of cortisolemia (r=0,74), respectively. There is a backwards correlation between the level of glycemia and insulin (r=-0,79).

**Dynamics of Situation Anxiety**

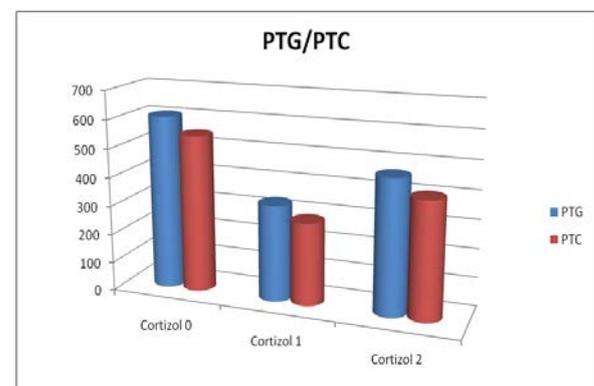
The situation anxiety in group As decreases significantly immediately after surgery, (p<0.0001 for TKA, THR respectively), the following day after surgery patients show slightly increased scores (p=0.0002 for TKA, p=0.0004 for THR) in comparison to the end of surgery, but significantly low compared to the preoperative moment (p<0.0001 for TKA, THR, respectively).

The situation anxiety presents a similar dynamics, the decrease being significant immediately after surgery (p=0,00011 for TKA and p<0,0001 for THR), but lower than in group As, and comes back to the preoperative value the next day after surgery. The diagram presenting the correlations between the level of situation anxiety and the value of cortisolemia in dynamics is representative both for TKA and for THR, the impact of sedation and anxiolysis being evidential in group As patients. Sedation Level Evaluation: TKA-2,3±0,35; THR-2,7±0,40 (altered Wilson scale).

**Dynamics of Cortisolemia**

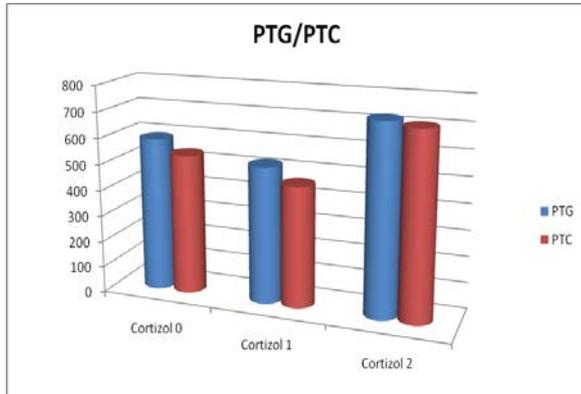
In the patients who benefited from intraoperative sedation and postoperative anxiolysis (Group As), both for TKA and for THR, the level of cortisolemia significantly decreases immediately after surgery (p<0.0001 for TKA, THR, respectively), increasing the following day after surgery (p<0.0001 for TKA, p=0,001 for THR, respectively), but maintaining itself at a lower level than before surgery.

The comparative diagram is representative:



**Fig. 1. Dynamics of cortisolemia according to the type of surgery in group As.**

In group B, the level of cortisolemia decreases significantly immediately after surgery ( $p=0.00014$  for TKA and  $p<0.0001$  for THR) but significantly increases statistically the following day after surgery ( $p<0.0001$ , both for TKA and for THR).

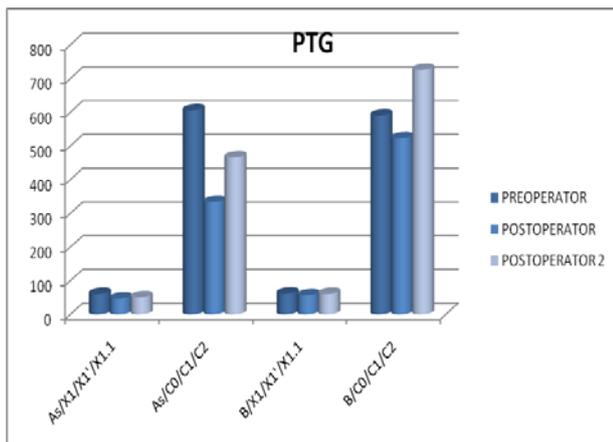


**Fig.2. Dynamics of cortisol according to the type of surgery in group B**

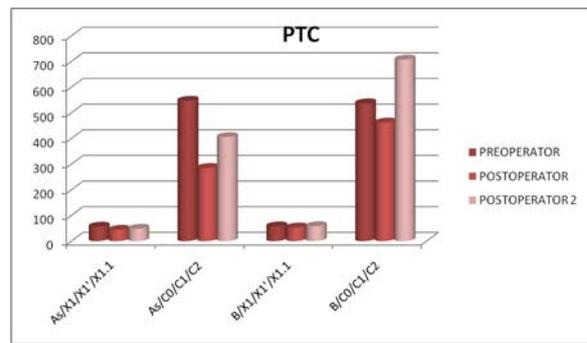
In the case of TKA patients, the level of Co1 decreases by 44.87% in the patients who benefited from sedation and only by 11.4% in the patients in group B.

In the THR patients, there may be seen the similar tendency, the decrease being higher in the case of patients sedated intraoperatorily (47.87% in comparison to 13.9%).

The level of situational anxiety preserves the same dynamics with that of cortisolemia, being lower in sedated patients in group As: 22,1% for TKA, 21,84% for THR, in comparison to group B (8,05% for TKA, 7,2% for THR).



**Fig.3. Dynamics of situation anxiety and cortisolemia compared in the two groups of TKA patients.**

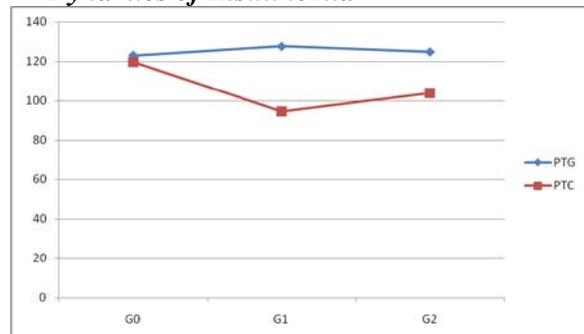


**Fig.4. Dynamics of situation anxiety and cortisolemia compared in the two groups of THR patients.**

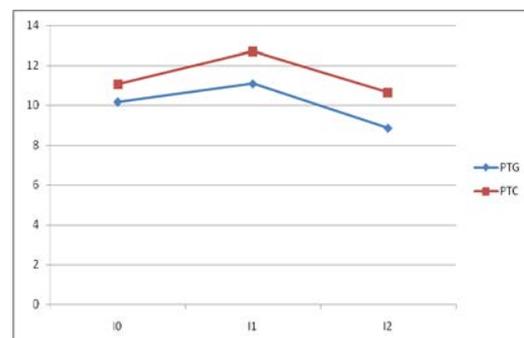
### Dynamics of Glycemia

Serica glycemia is maintained relatively stable (even decreasing in the case of THR ( $p=0.00014$ ) immediately after surgery in the patients in group As. Instead, in group B, the level of glycemia immediately after surgery is significantly increased ( $p<0.0001$ ) in patients with TKA, and not very significant ( $p=0.089$ ) in patients with THR. The following day after surgery, the values of glycemia maintain significantly high compared to the preoperative moment (G0) in TKA patients in group B ( $p<0.0001$ ).

### Dynamics of Insulinemia



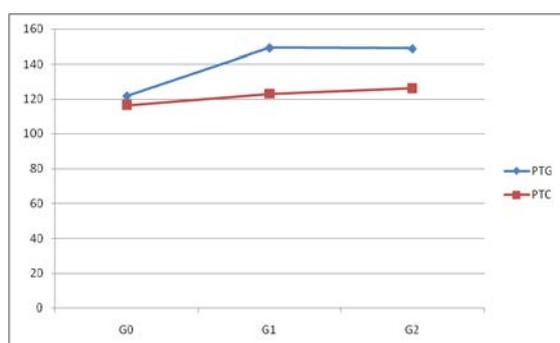
**Fig.5. Dynamics of glycemia in patients in group As according to the surgery**



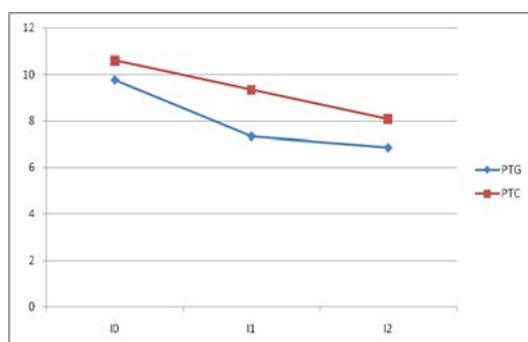
**Fig. 6. Dynamics of insulin in patients in group As according to the surgery**

In the As group, both for TKA and for THR, the dynamics of insulinemia has got an increasing-decreasing tendency, increases immediately after surgery ( $p=0,459$  for TKA,  $p=0,176$  for THR, respectively) and decreases the following day after surgery ( $p=0,0414$  for TKA,  $p=0,0049$  for THR, respectively).

In group B the tendency is different, thus insulin decreases progressively, both for TKA and for THR. There appears a significant statistically difference between the preoperative values and postoperative ones the next day after surgery ( $p=0,0154$  for TKA,  $p=0,010$  for THR, respectively).



**Fig.7. Dynamics of glycemia in patients in group B according to the surgery**



**Fig.8. Dynamics of insulin in patients in group B according to the surgery**

## Discussions.

The patients included in the study present a high level of anxiety and maintain/increase this level when faced with surgery (situation anxiety). Immediately before surgery, there may be seen a direct important correlation in the study: situation anxiety-cortisolemia-glycemia, both in patients suffering from coxarthrosis and in those with gonarthrosis. Glucocorticoids play an essential part in the glucidic metabolism, thus reinforcing the effects of other hormones involved in neoglucogenesis (glucagon and catecholamines), and inhibiting the absorption of peripheral glucose through insulin resistance, the main consequence being hyperglycemia (8);

therefore, a direct significant correlation between cortisolemia and glycemia may be justified. There is also another important correlation: situation anxiety-glycemia and, especially, situation anxiety-cortisolemia.

Activation of the hypothalamus-pituitary-adrenal axis (HPA) as a response to surgery may be altered by anaesthesia (9). Control of intraoperative pain (sufficient analgesia within the surgical field analgesy) and prevention of stress response do not appear as directly linked (confirmed by this study, as well), while the intraoperative analgesy does not allow to avoid the stress response, due to the incomplete suppression of sympathetic and somesthetic afferences. Nociception ways are only partially responsible for the stress response (9). In this sense, sedation and anxiolysis after rachianaesthesia may be beneficial.

Intraoperative sedation of patients with rachianaesthesia is not usually used (only 36% of the patients with rachianaesthesia for TKA benefited from sedation, in a recent French multicentral national study) (6).

The presence of old age and comorbidity of proposed patients for total articular arthroplasty impose high caution, even exaggerated sometimes, from some anaesthetists, especially where monitoring conditions are deficient.

The study shows the impact that undelines the necessity of sedation and anxiolysis in patients with high and very high preoperative anxiety, subjected to total arthroplasty at the level of the inferior limb. The level of cortisolemia, at the end of surgery, decreases about 3.5 times more in sedated patients, comparatively to its decrease in the case of non-sedated patients, in both types of arthroplasties. Rachianaesthesia is responsible for cortisolemia decrease at the end of surgery (in comparison to the preoperative moment) in non-sedated intraoperative patients, thus confirming that the neuraxial blockage through regional anaesthesia (spinal or epidural) stresses the HPA response (10).

The level of anxiety preserves a similar dynamics, decreasing about 2.8 times more in sedated patients, in comparison to anxiety decrease in non-sedated patients. There has to be pointed out that, although the used doses of midazolam and propofol

maintained a conscious level of sedation (altered Wilson score  $\leq 3$ ), the impact on the level of anxiety and cortisolemia was obvious, while the cardio-respiratory adverse effects were minimal: only 2 patients required assisted ventilation on the orofacial mask, for a few seconds.

The impact of anxiolysis is obvious the following day after surgery, as well. The level of cortisolemia increases in both groups, no matter the type of surgery (TKA/THR), in a direct correlation with the level of situational anxiety. There is also confirmed the fact that central blocks are associated with the decrease of cortisolemia level only during and after surgery (11). The patients who did not receive postoperative anxiolysis show an anxiety score similar to that before surgery, although the stressing event (the surgery) passed. Postoperative pain, sleep deprivation, the staff behaviour, but especially the fear for mobilization (the patients being told that they would start mobilization before evaluating anxiety X1.1) are definitely factors that contribute to the maintaining of a high level of situational anxiety. In the patients who received postoperative anxiolytic, the level of anxiety, even though it increases compared to the immediate moment after surgery, it remains at a significantly low level compared to the preoperative level. Immediately after surgery, in patients with THR, the tendency of glycemia is to maintain constant/ even low (especially in sedated patients). Instead, in patients with TKA, the tendency of glycemia is to increase, especially in non-sedated patients. The next day after surgery there is maintained the same tendency of seric glycemia in comparison to the immediate preoperative level. The anaesthetic modulation may have a direct effect (midazolam) or indirect (adrenergic blockage) upon the insulin dynamics.

Except for glycemia, situation anxiety and variables of endocrine stress follow a similar dynamics, in both types of prostheses included in the study. Thus, it is confirmed the study of G. M. Hall, according to which the patients with TKA present a significant glycemia increase, but there are no significant differences of the

cortisolemia level, compared to the patients with THR (12).

## CONCLUSIONS

Immediately after surgery, faced with surgery, there is a significant correlation: situation anxiety-cortisolemia-glycemia. The average values of glycemia and cortisolemia cross over the superior laboratory reference threshold.

Intraoperative sedation and postoperative anxiolysis in patients with high anxiety may indirectly modulate the postoperative neuroendocrine response, through anxiety modulation.

The propofol- midazolam combination is very satisfactory, the adverse effects being minimum in the old population with comorbidities.

Patients with high anxiety maintain a high postoperative level of anxiety, although the event considered as a major stress factor passed; other postoperative factors (mobilization, for example) should not be neglected, postoperative anxiolysis showing its utility in these patients.

Patients with TKA present a significantly high postoperative glycemia, in comparison to the THR patients.

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