Stress-induced Perioperative Depressive Symptoms

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Sustained stress has been correlated with increases in cortisol levels and decreased levels of brain transmitters including serotonin or dopamine. As a result of better understanding of human pathophysiology and pain physiology, the fields of surgery and anesthesia have seen major advances in the last years.However, a high percentage of patients develop depressive symptoms following major surgery and pathogenic perspective is very complex and require an holistic approach.

Keywords: stress, salivary cortisol, surgery, depression

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Over the years, the fields of surgery and anesthesia have seen major advances as a result of better understanding of human pathophysiology and pain physiology, development of new diagnostic tools, safer anesthetic agents and improvements in surgical techniques, such as minimally invasive surgery [1, 2]. The increased quality of surgical procedures and anesthesia has substantially reduced the risks and complication rates, which should help in enhancing the recovery of the surgical patient [3, 4].

Depressive symptoms are common adverse effects following surgical procedures [5]. Besides the pain and discomfort after surgery the patient may feel functional disturbances like loneliness, anxiety, fatigue or insomnia [6, 7]. Unfortunately, the majority of these symptoms are silent and frequently underdiagnosed; therefore patients often remain untreated [8, 9].

In recent years attention has been increasingly directed from the pathogenic perspective to an holistic approach of the medical and surgical practices involving psychosomatic medicine, whose main purpose is to reduce the incidence of depressive symptoms and their consequences in the postoperative period [10, 11].

The stress-depression connection: does stress cause depression?

In daily life we are exposed regularly to psycho-physical arousals which may be highly adaptive from the evolutionary point of view, since they promote coping with comparable situations in the future. However, be a caregiver for a family member with cancer, taking care of a parent with Alzheimer's, losing a job or the death of a loved one – are among those events which might lead to major depression in susceptible people. Any stressor elicits the activity of the body's stress-response mechanism. Sustained or chronic stress can lead to elevated cortisol, the *stress hormone*, levels and reduced serotonin and other neurotransmitters levels in the brain, including dopamine, which has been linked to depression. When these neurotransmitters are working normally, they regulate sleep, appetite, energy, and biological processes, and allow normal moods and emotions to express themselves. When the hypothalamus fails to turn on and off the production of stress hormones after a difficult situation, it can lead to depression in susceptible people.

Activation of the HPA axis and autonomic nervous system (ANS) activities are essential adaptive mechanisms that enable the human body to maintain physiological stability in response both to general stressful signals and to more specific (disease-induced) stimuli. The two systems coordinate, among others, the response of the immune and cardiovascular systems, bringing the body to homeostasis through the allostatic adaptation. An inappropriate behavioral adaptation to stressors is an important risk factor for depression in susceptible individuals (allostatic overload). Complex reciprocal counterbalances between HPA axis and autonomic nervous system (ANS) have been described [11, 12]; their chronic stimulation and dysregulation by stress may cause metabolic abnormalities.

The cortisol-depression connection

Cortisol is the primary end-product of the HPA axis since it is widely considered as a biological regulator of adaptation and of the maintenance of homeostasis in response to psychological andphysiopathological challenges [9, 10, 13]. Cortisol plays pathophysiologically a crucial role in the organism effort to respond/adapt to stressors.Cortisol binds to glucocorticoid receptors present in almost every tissue of the body. Consequently, cortisol mediates many metabolic processes ranging from induction of mobilization of energy, increasing cerebral perfusion rates and local glucose utilization, enhancing cardiovascular output and respiration, redistributing blood flow, increasing substrate and energy delivery to the brain and muscles, to modulating the immune function.

Substantial evidences exist to indicate a prominent role for chronically elevated levels of cortisol and a dysfunctional feedback system within the hypothalamic-pituitary-adrenal (HPA) axis in major depressive disorder [14-16]. However, it is well accepted also the opposite:

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that a hyporesponsive HPA axis is linked to increased susceptibility to chronic illness [17, 18]. Cortisol secretion is characterized by a circadian fluctuation, with the concentrations in the morning significantly higher than those measured in the evening. Moreover, a typical feature of cortisol production at the awake has also been recognized: the Cortisol Awake Response (CAR);as if there is a cycle within a cycle, CAR reflects changes in the cortisol concentration that occur during the first hour after wakening from sleep in the morning [18-20].

The salivary α-Amylase-depression connection

The search for a *cortisol similar* non-invasive and easily obtainable marker of the autonomic nervous system has raised salivary α-amylase (sAA) as a promising candidate. Salivary α-amylase is an enzyme important for carbohydrate digestion and its secretion is under strong neurohormonal control (i.e. released upon sympathetic stimulation).ANS activity could be studied through salivary α-amylase circadian fluctuation and production measured at the same time point of cortisol [19, 21-24]. The major advantage of sAA over other parameters reflecting sympathetic nervous system activity (i.e., heart rate measures or skin conductance) is that it is saliva-based. Salivary cortisol and α-amylase production are characterized by a circadian fluctuation [21, 23, 25, 26]. Salivary samples are relatively easy to obtain and can be collected at all times without being reliant on the assistance of medical staff.Previous studies from our group and others have shown that the measurement of salivary biomarkers is becoming more widely accepted for monitoring changes in HPA and ANS activity under physiopathological stress-related conditions [27-29]. Changes in salivary cortisol and α-amylase, as well as their diurnal fluctuations, are thought to have implications for health. The validity of using sAA as a marker of ANS in psychopathological conditions has been recently confirmed [30-32].

Causes for postoperative depression. The stress-depression connection: does stress cause depression?

Given the high prevalence of depressive disorders in the general population, it is not surprising that a high percentage of patients develop depressive symptoms following major surgery [5, 8].

Stress from surgery may psychologically and physiologically influence patients and can trigger depressive symptoms in the postoperative period [12]. The type of surgery and anesthesia used and the extent of the procedure can generate stress-related abnormalities that may, in turn, lead to metabolic disorders [13, 14]. In the immediate period (hours, days) after major surgery, a certain level of dysphoria is bound to appear, particularly after the effects of anesthesia have worn off. During this time patients often experience pain, discomfort, fatigue, disappointment or abandonment. This reaction has been compared with the postpartum blues experienced by new mothers in the first few days after delivery [15].

Many patients facing surgery naturally feel anxious and even scared about the course of their procedure. The fear of the operation, of being exposed, the pain and discomfort they might feel after the procedure and the uncertainty regarding the future can easily influence patients' abilities to cope with rehabilitation in the postoperative period [16, 17]. The extent of knowledge the patient has about the surgery and their ability to receive and absorb information has also been found to influence the feelings of anxiety and depression in the postoperative period [7].

Moreover, for many young patients facing surgery, the feelings of mortality and vulnerability can be profound and can shatter their self-image of power and confidence [18].

An important factor to be considered is the unpredictable nature of patient' reactions to surgery. Several studies have showed that postoperative depression depends on gender, age, beliefs or psychosocial status [6, 19, 20].

Preoperative evaluation traditionally assesses possible preexistent pathologies such as cardiovascular disorders, diabetes, renal or hepatic failure that could generate perioperative complications [21]. However, little attention is being paid to the psychological profile of the patient facing major surgery. Previous studies have shown that underlying psychiatric conditions significantly increase the risk for postoperative anxiety and depression [22-24].In fact, be a caregiver is among those events which mightlead to major depression: any stressor elicits the activity of the body's stress-response mechanism.

Activation of the HPA axis and autonomic nervous system (ANS) activities are essential adaptive mechanisms that enable the human body to maintain physiological stability in response both to general stressful signals and to more specific (disease-induced) stimuli. The two systems coordinate, among others, the response of the immune and cardiovascular systems, bringing the body to homeostasis through the allostatic adaptation. An inappropriate behavioral adaptation to stressors is an important risk factor for depression in susceptible individuals (allostatic overload). Complex reciprocal counterbalances between HPA axis and autonomic nervous system (ANS) have been described [11, 12]; their chronic stimulation and dysregulation by stress may cause metabolic abnormalities.

Why and how prevent postoperative depression?

Postoperative depression does not influence only the individual, but has a negative impact also on health services and society. Also, it has been shown that the consequences of untreated postoperative depressive symptoms have been shown to impact the life of the individual up to 5 years after the surgery [22].

The detrimental effects of poor psychological adjustment following surgical procedures generate increased costs due to frequent hospital readmissions higher complication rates and extensive treatments [15, 21].

Poorer psychological recovery can lead to physical impairments, which can, in turn, cause higher rates of unemployment and disability pension. Depressed patients are more likely to have lower rates of returning to work and longer sickness absence [17].

New progresses have been made for accelerating recovery after surgical procedures, leading to shorter hospital stays, decreased complication rates and a faster return to the normal functioning and, therefore, increased safety and satisfaction after discharge. This led to the development of the concept of "fast-track" surgery, which involves coordinated efforts for preoperative patient education, adequate pain relief, reduction of surgical stress, early enteral nutrition and rapid mobilization. This new surgical approach has been shown to provide good results in terms of quality of life for patients undergoing surgery [2, 10].

This, however, does not guarantee the elimination of patient postoperative anxiety and depressive symptoms. Psychological interventions during the preoperative period may help in reducing the risk of postoperative depression,

which could facilitate the clinical and psychological recovery [28].

These types of accelerated recovery programs require the organization of a multidisciplinary team, including not only surgeons and anesthesiologists, but also nurses, physical therapists, psychologists, psychiatrists and gerontologists [1]. To this end, there is a need for increased awareness among healthcare professionals of the risks and consequences of postoperative depression.

Reducing the incidence of depression following surgery involves first a thorough preoperative clinical and psychological examination of the patient to detect underlying psychiatric conditions that may erupt in postoperatively. Furthermore, preoperative education and psychological preparation has a major role in modifying patient's response to the operative experience [28].

Psychological interventions involving deep breathing, muscle relaxation and psychotherapy have been shown to be particularly useful for surgical patients in reducing postoperative distress, pain, and length of hospital stay [29].

When patients experience depressive symptoms following surgery, their ability to cope with rehabilitation may be impaired. This is frequently associated with adverse outcomes in the postoperative period.

Studies have shown that surgical patients who are depressed are more likely to have a poorer recovery in functional status compared to non-depressed patients. This leads to longer hospital stays and more frequent rehospitalizations after discharge [15].

A poor psychological adjustment after surgery has been associated with a higher risk of postoperative complications. Depressive symptoms experienced during the recovery period have been shown to increase the risk of cardiovascular events and decrease survival. Furthermore, increased lengths of hospitalization and further treatments for postoperative complications translate into higher costs for the society [6, 17].

Patient compliance and adherence to treatments is also thought to be affected by their mood in the postoperative period. Emotional distress following surgery also have a detrimental effect on physical recovery and patient ability to reintegrate into society. Postoperative depression was linked to a greater risk of disability, decreased social functioning and performance [7, 22, 25, 26].

Delirium is another condition that can arise during the first few days after surgery, particularly among elderly people. Much like depression, postoperative delirium has been found to be an important predictor for long-term disabilities such as dementia and cognitive dysfunction and an independent risk factor for increased mortality [27, 28].

Conclusions

Even with major improvements in the fields of anesthesia and surgery, which have made surgical procedures less invasive, less traumatic and more reliable, depressive symptoms are still a commonly experienced and feared adverse effect in the postoperative period [3, 4, 8].

The medical staff should be aware of the possible risks and consequences of postoperative depression, while a multidisciplinary collaboration should be established between surgeons, anesthesiologists, nursing staff, physiotherapists, psychologists, psychiatrists and gerontologists in order to obtain a successful recovery.

A thorough preoperative assessment of emotional status could predict the level of emotional distress after surgery. Psychological interventions and patient education during the preoperative period may help in reducing the risk of postoperative depression, thus facilitating the clinical and psychological recovery [7,29]: psychosomatic interventions for postoperative stress reduction could facilitate recovery and significantly improve patient well-being [30, 31,37-43].

Whether stress is acute or chronic, it can affect the levels of Cortisol and a-Amylase which are measurable with a range of sampling regimens and sample types. Today, the most commonly used sample specimen in stress research is human saliva [32-36]. It has been extensively integrated within the scientific field to assess the levels of 'free' steroid and sex hormones, and correlation of these hormones with circulating levels in serum has been well established in the literature.

Acknowledgements: This work was partially supported by the European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/136893 to LD. #These authors participated in this study respectively as student of the XXXII and XXXI Cycle of the Doctorate in Pharmacology and Toxicology, held at the Department of Physiology and Pharmacology – Sapienza University of Rome.

References

1.KEHLET, H., WILMORE, D.W. Evidence-based surgical care and the evolution of fast-track surgery. Ann. Surg., 248, nr. 2, 2008, 189-198.
2.FEARON, K.C., LJUNGQVIST, O., VON MEYENFELDT, M., et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin.Nutr.,24, nr. 3, 2005, 466-477.
3.WILMORE, D.W. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Ann. Surg., 236, nr. 5, 2002, 643-648.
4.GIANNOUDIS, P.V., DINOPOULOS, H., CHALIDIS, B., HALL, G.M. Surgical stress response. Injury., 37, Suppl 5, 2006, S3-9.
5.POOLE, L., KIDD, T., LEIGH, E., et al. Depression, C-reactive protein and length of post-operative hospital stay in coronary artery bypass graft surgery patients. Brain.Behav. Immun., 37, 2014, 115-121.
6.MCKENZIE, L.H., SIMPSON, J., STEWART, M. A systematic review of pre-operative predictors of post-operative depression and anxiety in individuals who have undergone coronary artery bypass graft surgery. Psychol. Health. Med., 15 nr. 1, 2010, 74-93.
7.JONSSON, C.A., STENBERG, A., FRISMAN, G.H. The lived experience of the early postoperative period after colorectal cancer surgery. Eur. J. Cancer. Care.(Engl)., 20, nr. 2, 2011, 248-256.
8.FOSS-NIERADKO, B., STEPNOWSKA, M., PIOTROWICZ, R. Effect of the dynamics of depression symptoms on outcomes after coronary artery bypass grafting. Kardiol. Pol., 70, nr. 6, 2012, 591-597.
9.ADACHI, Y., KIMURA, H., SATO, N., et al. Preoperative level of depression is a predictor of postoperative levels of depression in patients with head and neck cancer. Jpn. J. Clin. Oncol., 44, nr. 4, 2014, 311-317.
10.KEHLET, H., DAHL, J.B. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet.,362, nr. 9399, 2003, 1921-1928.
11.LEWICKA M., MAKARA-STUDZINSKA, M., SULIMA, M., WIKTOR, H. Intensification of anxiety and depression, and personal resources among women during the peri-operative period. Ann. Agric. Environ. Med., 21, nr. 1, 2014, 91-97.
12.AMIRI, F., GHOMEISHI, A., ASLANI, S.M., et al. Comparison of surgical stress responses during spinal and general anesthesia in curettage surgery. Anesth. Pain.Med., 4, nr. 3, 2014, e20554.
13.BRODNER, G., VAN AKEN, H., HERTLE, L., et al. Multimodal perioperative management-combining thoracic epidural analgesia, forced mobilization, and oral nutrition-reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesth.Analg., 92, nr. 6, 2001, 1594-1600.

14.DAMIAN, L., SAPONARO, A., PATACCHIOLI, F.R. Endocrine profiles of depressive symptoms.The.Art.Of.Healing., 3-4(XXXI), 2015.
15.NICKINSON, R.S., BOARD, T.N., KAY, P.R. Post-operative anxiety and depression levels in orthopaedic surgery: a study of 56 patients undergoing hip or knee arthroplasty. J. Eval. Clin.Pract., 15, nr. 2, 2009, 307-310.
16.CAUMO, W., SCHMIDT, A.P., SCHNEIDER, C.N., et al. Risk factors for postoperative anxiety in adults. Anaesthesia.,56, nr. 8, 2001, 720-728.
17.MCCRONE S., LENZ, E., TARZIAN, A., PERKINS, S. Anxiety and depression: incidence and patterns in patients after coronary artery bypass graft surgery. Appl.Nurs. Res., 14, nr. 3, 2001, 155-164.
18.WEIDNER, K., ZIMMERMANN, K., NEISES, M., et al. Effects of psychosomatic interventions within the consultation service of a gynecological university hospital. Psychother.Psychosom. Med. Psychol., 56, nr. 9-10, 2006, 362-369.
19.ESTEGHAMAT, S.S., MOGHADDAMI, S., ESTEGHAMAT, S.S., et al. The course of anxiety and depression in surgical and non-surgical patients. Int. J.Psychiatry. Clin.Pract., 18, nr. 1, 2014, 16-20.
20.AI, A.L., PETERSON, C., BOLLING, S.F., RODGERS, W. Depression, faith-based coping, and short-term postoperative global functioning in adult and older patients undergoing cardiac surgery. J.Psychosom. Res., 60, nr. 1, 2006, 21-28.
21.KEHLET, H., WILMORE, D.W. Multimodal strategies to improve surgical outcome. Am. J. Surg., 183, nr. 6, 2002, 630-641.
22.PAKARINEN, M., VANHANEN, S., SINIKALLIO, S., et al. Depressive burden is associated with a poorer surgical outcome among lumbar spinal stenosis patients: a 5-year follow-up study. Spine. J., 14, nr. 10, 2014, 2392-2396.
23.SINIKALLIO, S., AALTO, T., AIRAKSINEN, O., et al. Depressive burden in the preoperative and early recovery phase predicts poorer surgery outcome among lumbar spinal stenosis patients: a one-year prospective follow-up study. Spine., 34, nr. 23, 2009, 2573-2578.
24.URBAN-BAEZA, A., ZARATE-KALFOPULOS, B., ROMERO-VARGAS, S., et al. Influence of depression symptoms on patient expectations and clinical outcomes in the surgical management of spinal stenosis. J.Neurosurg. Spine., 22, nr. 1, 2015, 75-79.
25.HORNE, D., KEHLER, D.S., KAOUKIS G., et al. Impact of physical activity on depression after cardiac surgery. Can. J.Cardiol., 29, nr. 12, 2013, 1649-1656.
26.BRYCZKOWSKI, S.B., LOPREIATO, M.C., YONCLAS, P.P., et al. Delirium prevention program in the surgical intensive care unit improved the outcomes of older adults. J. Surg. Res., 190, nr. 1, 2014, 280-288.
27.LACATUSU, C., CIJEVSCHI-PRELIPCEAN, C., MIHAI, C., MIHAI, B. Ethics of artificial nutrition. Rev. Rom.Bioet., 12, nr. 1, 2014, 44-55.
28.CEREJEIRA, J., BATISTA, P., NOGUEIRA, V., et al. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 axis. J.Geriatr. Psychiatry. Neurol., 26, nr. 3, 2013, 185-194.
29.KAVAKCI, O., ALTUNTAS, E.E., MUDERRIS, S., KUGU, N. Effects of the preoperative anxiety and depression on the postoperative pain in ear, nose and throat surgery. Indian. J. Otol., 18, 2012, 82-87.
30.BROADBENT, E., KAHOKEHR, A., BOOTH, R.J., et al. A brief relaxation intervention reduces stress and improves surgical wound healing response: a randomised trial. Brain.Behav. Immun., 26, nr. 2, 2010, 212-217.
31.CIUBOTARIU, D., GHICIUC, C.M., LUPUSORU, R.V., et al. Experimental research showing the beneficial effect of oral zinc administration in opioid tolerance. Farmacia, 63, nr. 6, 2015, 835-839.
32.COZMA, S., GHICIUC, C.M., DAMIAN, L., et al. Distinct activation of the sympathetic adreno-medullar system and hypothalamus pituitary adrenal axis following the caloric vestibular test in healthy subjects. PloS. One.,13, nr. 3, 2018, e0193963.
33.COZMA, S., DIMA-COZMA, L.C., GHICIUC, C.M., et al. Salivary cortisol and α-amylase: subclinical indicators of stress as cardiometabolic risk. Braz. J. Med. Biol. Res., 50, nr. 2, 2017, e5577.
34.DAMIAN, L., GHICIUC, C.M., DIMA-COZMA, L.C., et al. No definitive evidence for a connection between autoimmune thyroid diseases and stress in women. Neuro. Endocrinol. Lett., 37, nr. 3, 2016, 155-162.
35.DIMA COZMA, C., PATACCHIOLI, F.R., GHICIUC, C.M., et al. Current perspectives in stress research and cardiometabolic risk. Rev.Cercet.Interv. Soc., 45, 2014, 175-188.
36.COZMA, S., MARTU, C., GHICIUC, C.M., et al. Salivary α-amylase activity - a novel non-invasive biomarker in clinical pathology. Rev. Chim.(Bucharest), **69**, no. 3, 2018, p. 728-730.
37.COMAN ,M., CHISCOP ,I., MATEI, M.N., Dynamics of biochemicalchanges in viral B Virus Hepatitis, Rev. Chim. (Bucharest), **66**, no. 12, 2015, p. 2144-2146
38.ARDELEANU, V., NECHITA, A., FRANCU, L.L., et al., Nuclear morphometryandproliferatveactivityevaluation in the gastrointestinal stromaltumors, Romanian Journal of Morphologyandembryology, 55(2), 2014, pg.319-33
39.ANTOHE M.,ANDRONACHE M, FEIER R, STAMATIN O, FORNA NC, Statistical studies regarding therapeutic approaches for edentulous social clinical cases in student„spractical stages, Romanian Journal of Oral rehabilitation, 9(2),2017,94-99
40.POPESCU, E., AGOP FORNA,D., EARAR, K., FORNA, N.C., Bone substitutes used in guided bone regeneration technique review, Mat. Plast., **54**, no.2, 2017, p. 390-392
41.ANTOHE, M.E.,AGOP FORNA, D., DASCALU, C.G., FORNA,N.C., Implications of digital image processing in the paraclinical assessment of the partially edentated patient, Rev.Chim. (Bucharest), **69**, no.2, 2018, p.521-524
42. AGOP FORNA, D.**,** FORNA, N.C., EARAR, K., et al., Postoperative clinical evolution of edentulous patients treated by guided bone regeneration using xenograft bone substitute and collagen membrane, Mat.Plast., **54**, no.2, 2017, p.312-315
43.LOGHIN, I., EARAR, K., NECHITA, A., et.al.,Chemistry of active endocardidis preserving wih vegetation on the prosthetic valve, Rev.Chim.(Bucharest), **66**, no.3, 2015, p. 387-389

Manuscript received: 13.08.2018