HEPMP

HIGHER EDUCATION PAIN MEDICINE PROJECT

Effects of Psychological Interventions on Surgical Outcomes

Project title	Strengthening Capacities for Higher Education of Pain Medicine in Western Balkan countries
Project acronym	HEPMP
Project reference number	585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP
Coordinator	University of Belgrade
Project start date	October 15, 2017
Project duration	36 months

Reference no and title of work package	WP2. Development of joint curricula for PM study program
Institution	The University of Florence
Author(s)	G. Villa
Document status	Final
Dissemination level	Public

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

This project has been funded with support from the European Commission.
This publication [communication] reflects the views only of the author, and the Commission cannot be held responsible for any use which ma y be made of the information contained therein.

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List of Abbreviations

CBHE	Capacity Building in Higher Education
D&E	dissemination and exploitation
EACEA	Education, Audiovisual and Culture Executive Agency
EC	European Commission
EU	European Union
GA	Grant Agreement
HCWs	Health Care Workers
HE	Higher Education
HEI	Higher Education Institution
HEPMP	Higher Education Pain Medicine Project
LLL	Life Long Learning
NEO	National Erasmus+ Office
PA	Project Adviser
PA	Partnership Agreement
PC	Project Coordinator
PCC	Partner Country Coordinator
PCs	Partner Countries
PCT	Partner Country Team
PgCC	Programme Country Coordinator
PgCs	Program Countries
PgCT	Programme Country Team
PM	Pain Medicine
PMB	Project Management Board
QCB	Quality Control Board
TL	Task Leader
TLs	Task Leaders
UB	Faculty of Medicine University of Belgrade, Belgrade, Serbia
UBBL	Faculty of Medicine University of Banja Luka, Bosnia and Herzegovina
UF	Faculty of Medicine University of Florence, Italy
UHDM	University Clinical Hospital Centre "Dr DragisaMisovic-Dedinje" Belgrade, Serbia
UK	Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia
ULj	Faculty of Medicine University of Ljubljana, Slovenia
UP	Faculty of Medicine University of Podgorica, Montenegro
UR	Faculty of Medicine University of Rijeka, Croatia
UT	Faculty of Medicine University of Tuzla, Bosnia and Herzegovina
WP	Workpackage

I About the HEPMP project

1.1 The HEPMP project summary

Funding: Erasmus+
Key Action: KA2 Capacity Building in Higher Education
Type of project: Joint Projects
Coordinating Institution: University of Belgrade

The main aim of HEMP project is to increase quality of education in pain medicine in order to contribute to the improvement of public health care services and PCs in line with the Health 2020. In Serbia, Montenegro and Bosnia and Herzegovina there is a significant problem of large percentage of the population who suffers from cancer, rheumatic and neurological diseases, while education in the field of pain medicine is insufficient. In fact, one of the priorities of the strategy Health 2020 improvement of the quality of medical services and continuously adapt to changing patterns of disease. Aim of this project is developing an interdisciplinary program in Pain Medicine at the under / postgraduate studies by applying new methodologies and specific learning outcomes in partner country universities. The introduction of the modernized study program of pain medicine is important for improvement of the quality of higher education that will contribute to improve the health care of the population. Moreover, one of the aims is establishment of academic network that would allow the exchange of knowledge of HCWs in Serbia, Montenegro and Bosnia and Herzegovina. The main tool of this network would be development of educational PAIN REGION WB Network which will enhance regional cooperation and education of pain medicine of all partner country universities.
Also, one of the HEPMP aims is delivering of trainings of pain medicine in order to increase skills and competences of health care workers (HCW) in PCs . Training would be for the two target groups: the first type of courses would be for HCWs who work in primary health care centres and daily dealing with the management of pain medicine, and other types of courses would organized in the form of highly specialized training for interventional treatment of pain for doctors who work in tertiary institutions. During the project will form the learning material in the form of brochures for courses and textbooks on pain.

1.2 The HEPMP project consortium

No	Institution	City	Country
1	University of Belgrade	Belgrade	Serbia
2	University of Kragujevac	Kragujevac	Serbia
3	University of Tuzla	Tuzla	Bosnia and Herzegovina
4	University of Banja Luka	Banja Luka	Bosnia and Herzegovina
5	University of Montenegro	Podgorica	Montenegro
6	University of Florence	Florence	Italy
7	University of Ljubljana	Ljubljana	Slovenia
8	University of Rijeka	Rijeka	Croatia
9	KBC Dr. Dragisa Misovic-Dedinje	Belgrade	Serbia

1.3 The HEPMP Managing Board

No	Name and Last Name	Institution
1	Prof. dr ***Predrag Stevanović***,	University of Belgrade, **Project Coordinator**
2	Prof. dr Jasna Jevđić	University of Kragujevac
3	Prof. dr Vladimir Đukić	KBC dr Dragiša Mišović
4	Prof. dr Danko Živković	University of Montenegro
5	Prof. dr Jasmina Smajić	University of Tuzla
6	Prof. dr Darko Golić	University of Banja Luka
7	Prof. dr Anđelo Rafaele De Gaudio	University of Florence
8	Prof. dr Maja Šoštarić	University of Ljubljana
9	Prof. dr Željko Župan	University of Rijeka

II Management of Surgical stress and postoperative pain: non-pharmacological interventions

2.1 Background

Postoperative complications and undesirable sequelae of surgery such as acute and chronic pain, fatigue, depression, and prolonged convalescence occur frequently, particularly in frail patients (Chelazzi et al. 2015). Their development is usually associated with a maladaptive stress response to surgical injury (H. Kehlet 1997). In some patients, surgical stress is amplified and/or prolonged to such extent as to overcome the functional reserve of organs (Kohl and Deutschman 2006). Under these conditions, tissue regeneration, body mass anabolism, immunological system, inflammation, and organ function recovery are impaired (Kohl and Deutschman 2006) and can lead to worsened patients' outcomes.

Several perioperative variables – including, for instance, blended anesthesia, opioids sparing strategies, or minimally invasive surgery) – seem to counteract the pathophysiological mechanisms underlying maladaptive surgical stress response. Nevertheless, no single surgical or anesthesiologic option has been demonstrated to be able to completely eliminate postoperative morbidity and mortality (H. Kehlet 1997; Henrik Kehlet and Ph 2000). Nowadays, comprehensive multimodal and multidisciplinary strategies have been developed to modulate the surgical stress response, reduce postoperative complications, "Enhance Recovery After Surgery", and improve patients' quality of life in the short- and long-term (Figure 1).

Non-physical, preoperative patient factors such as depression, anxiety, and catastrophizing attitudes have been recognized as strong predictors of surgical outcomes (Ellis et al. 2012; Rosenberger, Jokl, and Ickovics 2006; Theunissen et al. 2012). Patient behaviors (e.g. smoking, obesity, alcohol intake) and negative psychological states can both affect surgical recovery (Mavros et al. 2011). Moreover, non-physical, preoperative patient factors may directly affect the neuroendocrine and inflammatory response to surgical stress (Mavros et al. 2011), thus influencing perioperative immune function and surgical outcomes.

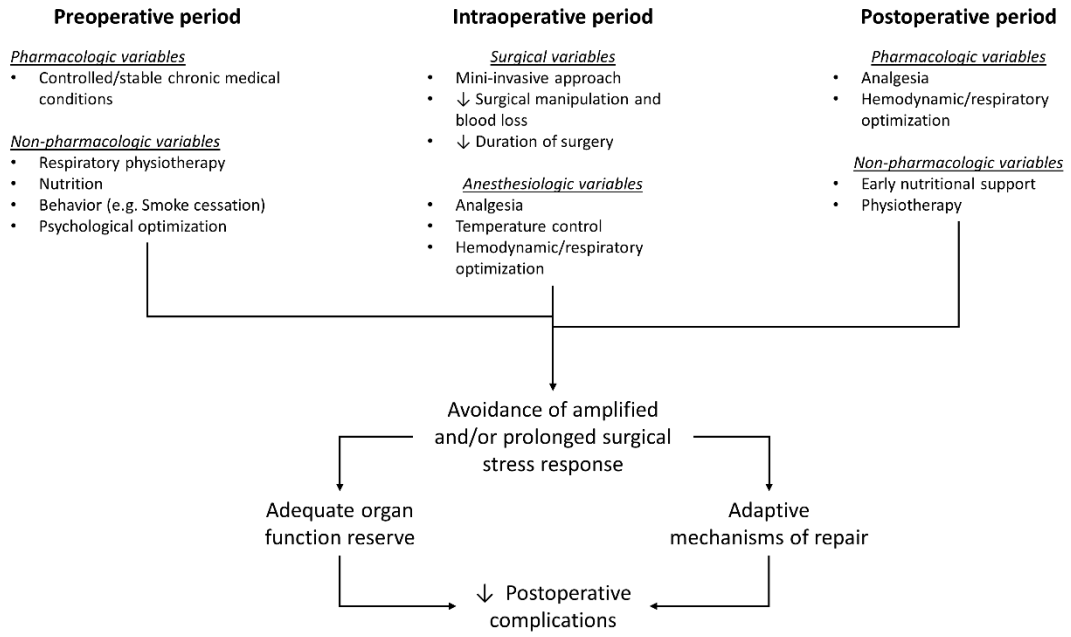

Fig 1. Preoperative, Intraoperative and Postoperative variables affecting the patient surgical stress response. This review specifically focuses on the effects of psychological optimization (i.e. a preoperative non-pharmacological variable) in reducing the surgical stress response.

Within this context, specific psychological interventions aimed at preventing maladaptive psychological features have been demonstrated to be effective in reducing the surgical stress response in surgical patients (E. a. Nelson et al. 2013). Cognitive-behavioral techniques and other interventions, such as relaxation, mindfulness-oriented tasks, support to adaptive coping strategies or hypnosis, as well as supportive care and narrative medicine-based interventions can realistically be adopted in perioperative care and surgical procedures, and should be considered a feasible option to improve clinical practice(Johnston and Vögele 1993; Powell et al. 2016).

Here we review for the HEPMP project research and issues that have been identified in psychology as relevant to surgical care and promote the perioperative integration of physical and non-physical interventions aimed at modulating the surgical stress response. Specifically, we will: 1) summarize current understanding of the pathophysiological mechanisms underlying maladaptive surgical stress response; 2) describe the impact of psychological features on neuro-chemical signaling during perioperative metabolic adaptation; 3) outline the clinical and metabolic effects that

the most common psychological approaches have on surgical patients when interventions such as cognitive-behavioral techniques and narrative medicine are applied perioperatively.

We performed a computerized search in the following electronic databases: the Cochrane Register of Controlled Trials, PubMed, EMBASE, PsycINFO, and CINAHL. The following search terms were used: 'surgery', 'relaxation therapy', 'mindfulness', 'cognitive behavioral therapy', 'coping', 'hypnosis', 'narrative medicine', 'psychological intervention', 'pain', and 'anxiety'. The inclusion criteria for eligibility of studies were: 1) papers reporting pain and/or anxiety among outcome measures; 2) papers published in English from Jan 2020 to Dec 2019. The following psychological interventions were considered: 1) Cognitive-Behavioral Therapies, 2) Relaxation techniques, 3) Mindfulness, 4) Narrative Medicine, 5) Hypnosis, 6) Coping strategies. Assessment of quality was done using the GRADE approach.

A total of 54 papers were deemed eligible for inclusion in this review for the HEPMP project. We have grouped the research findings under the following areas: Pathophysiological mechanisms of maladaptive surgical stress response; Psychological features and perioperative metabolic adaptation; and Psychological treatments, surgical stress, and outcomes.

2.2 Pathophysiological mechanisms of maladaptive surgical stress response

Stress can be defined as a "specific response by the body to a stimulus, such as fear or pain, that disturbs or interferes with the normal physiological equilibrium of an organism." It can be "external" (induced by environmental factors and social or psychological situations) or "internal" (due to illness or iatrogenesis, that is, resulting from a medical procedure). Accordingly, psychological or biochemical stress in the perioperative period can derive from environmental stressors as well as from surgical insult. Stress can trigger or influence the course of many medical conditions, including organic diseases (e.g. perioperative outcomes) or psychological disorders (e.g. depression and anxiety). It induces a standardized, non-species-specific, well organized, and predictable response, which is adaptive in nature and intended to provide an adequate amount of energy substrate and amino acids for the synthesis of visceral proteins and the healing process of the organism (Kohl and Deutschman 2006).

A physiological, balanced, and well controlled response is usually associated with

complete and rapid recovery from the surgical procedure. However, pre-existing diseases as well as the patient's genetic predisposition may induce a dysfunctional adaptation leading to an exaggerated inflammatory response (i.e. systemic inflammatory response syndrome, SIRS) or to an inadequate response (i.e. anergy) (Kohl and Deutschman 2006). The metabolic surgical stress response can be described as a functional adaptation which occurs in surgical patients and is sustained by the activation of trauma-induced neuroendocrine pathways and several inflammatory mediators (e.g. cytokines, arachidonic acid metabolites, complement, nitric oxide, and free oxygen radicals)(H. Kehlet 1997).

The neuroendocrine response is characterized by an increased secretion of cortisol and epinephrine, as well as of aldosterone, glucagon, growth hormone, and arginine-vasopressin. Hemodynamic and metabolic variations occurring during surgical stress events elicit a prompt secretion of epinephrine induced by activation of the sympathetic nervous system. Moreover, afferent impulses from the damaged tissue stimulate the secretion of hypothalamic releasing hormone with duration and amplitude correlated with the extent of the surgical trauma(Hogan et al. 2011; Kohl and Deutschman 2006). The endocrine response to surgical stress involves several hormonal axes beside the hypothalamic-pituitary-adrenal axis; it is well organized, self-limited, and mainly promotes metabolic adaptation during surgical stress [3,12]. Inflammatory mediators, and, in particular, cytokine response during stress events have been extensively studied. Typically, cytokines response is characterized by production and release of a wide range of pro-inflammatory mediators and their physiologic modulating compensatory substances, i.e. anti-inflammatory mediators. The co-expression of inflammatory and anti-inflammatory pathways, as well as the controlled predominance of their mediators with a specific timing after the surgical procedure, guarantee an adaptive inflammatory response and avoid disorders leading to SIRS or anergy. Furthermore, the release of cytokines regulates the immuno-inflammatory response triggered by the acute stressor event. In fact, cytokines promote communication among leukocytes by linking innate and adaptive immune responses (Matarese and La Cava 2004; Menger and Vollmar 2004).

Also, it has been demonstrated that the wide interaction between neuroendocrine and cytokine mediators can influence the regulation of the metabolic stress response (Hogan et al. 2011). For instance, Tumor Necrosis Factor (TNF)-a, Interleukin (IL)-1, and IL-6 induce the activation of the hypothalamic-pituitary-adrenal axis (van der Meer et al. 1995). In healthy subjects, the administration of TNF-a induces high plasma levels of cortisol, corticotropin, catecholamines, growth hormone and

glucagon, that is, a hormonal response comparable to that observed during stress events (Bach et al. 2015). Corticotropin-releasing hormone, which is released by the hypothalamus during the stressor event, is also produced by immune cells (Hendricks and Mashaly 1998). Finally, immune cells seem to act as a new and widely distributed adrenergic organ which generates and releases catecholamines (Cosentino et al. 2002).

It is worth noting that also psychological, perioperative patient factors such as psychological state and/or personality may directly affect the surgical stress response according to different mechanisms (Mavros et al. 2011). Interestingly, several studies have shown that these factors more accurately predict postoperative outcomes compared with surgical or anesthesiologic variables (Ellis et al. 2012).

2.3 Psychological features and perioperative metabolic adaptation

Negative psychological states indirectly influence patient behavior (e.g. obesity, smoking, alcohol intake) and may affect surgical recovery (Ellis et al. 2012). In particular, patients' psychological features may directly influence the inflammatory and neuroendocrine pathways underlying the surgical stress response (Ellis et al. 2012), with major repercussions on immunological perioperative state and surgical outcomes.

The activation of the autonomic nervous system during an acute stressor event may cause the sympathetic fibers to release a wide range of mediators directly affecting the immune response (Ader, Cohen, and Felten 1995). Moreover, the sensitivity and density of adrenergic receptors to different components of the immune system may affect the responsiveness of cell subsets to stressor events (Anstead et al. 1998). Similarly, the several hormones released through the stress-induced activation of the hypothalamic-pituitary-adrenal axis (e.g. the adrenal hormones epinephrine, norepinephrine, prolactin, cortisol, growth hormone and the brain peptides melatonin, β-endorphin, and enkephalin) may affect the immune response. In particular, these hormones may bind specific receptors to the immune cells and regulate their function and distribution (Ader, Cohen, and Felten 1995). Consequently, different patterns of activation may be identified during stressor events, with potentially adaptive upregulation of the natural immunity and downregulation of the specific immunity (Anstead et al. 1998; Segerstrom and Miller 2004). Based on a meta-analysis considering more than 300 papers, Segerstrom et al. described the pathophysiological relationship between hormonal

alteration during psychological stress and the immune system.

The relationship between psychological factors and inflammation (expressed as cytokine modulation) is well established in the literature (Glaser et al. 1999), also in the surgical setting (Broadbent et al. 2003). This relationship may lead to maladaptive mechanisms of perioperative inflammation and play a role in the development of postoperative complications. Similar to the neuroendocrine response, the cytokine response to surgical stress may also affect immune function. According to several studies, correlations do exist between psychological stress and reduced natural killer cell cytotoxicity, suppressed lymphocyte proliferation, and blunted humoral responses to immunization (Cohen, Miller, and Rabin 2001; Segerstrom and Miller 2004). An inadequate immune response is considered the main cause of high incidence of infections among chronically stressed individuals. Finally, a pathological pattern of cytokine secretion during stressor events has been recognized as one important aspect that may lead to an imbalance between cellular Th-1 and humoral Th-2 activation and, as a consequence, infectious/autoimmune diseases.

Importantly, the aforementioned psychoneuroendocrine characteristics and, more in general, the psychosomatic effects of psychological stress on inflammation and surgical response might be influenced by psychological treatments. Several studies have demonstrated that most psychological therapies are associated with increased secretion of inhibiting hypothalamic hormones, such as somatostatin or dopamine, and decreased secretion of releasing hormones, such as thyrotropin- and corticotropin-releasing hormones and the growth hormone-releasing factor (Jindal, Gupta, and Das 2013). Under such circumstances, cortisol levels decrease (Walton et al. 1995) whereas levels of beta-endorphins may increase (Jindal, Gupta, and Das 2013). A similar restoration of physiological neuroendocrine adaptation has also been observed. All these effects might positively contribute to modulate immune system functions during stress events, including surgery.

2.4 Psychological treatments, surgical stress, and pain

Psychological therapies encompass a wide range of interventions and approaches, such as cognitive-behavioral therapy and narrative medicine, aimed at facilitating the mind's capacity to influence physical health (Wolsko et al. 2004). These treatments, used during psychotherapy or clinical psychology, might have a positive effect on the patient's perioperative perception of emotions, cognitions, and

behaviors, thus influencing surgical outcomes (Figure 2).

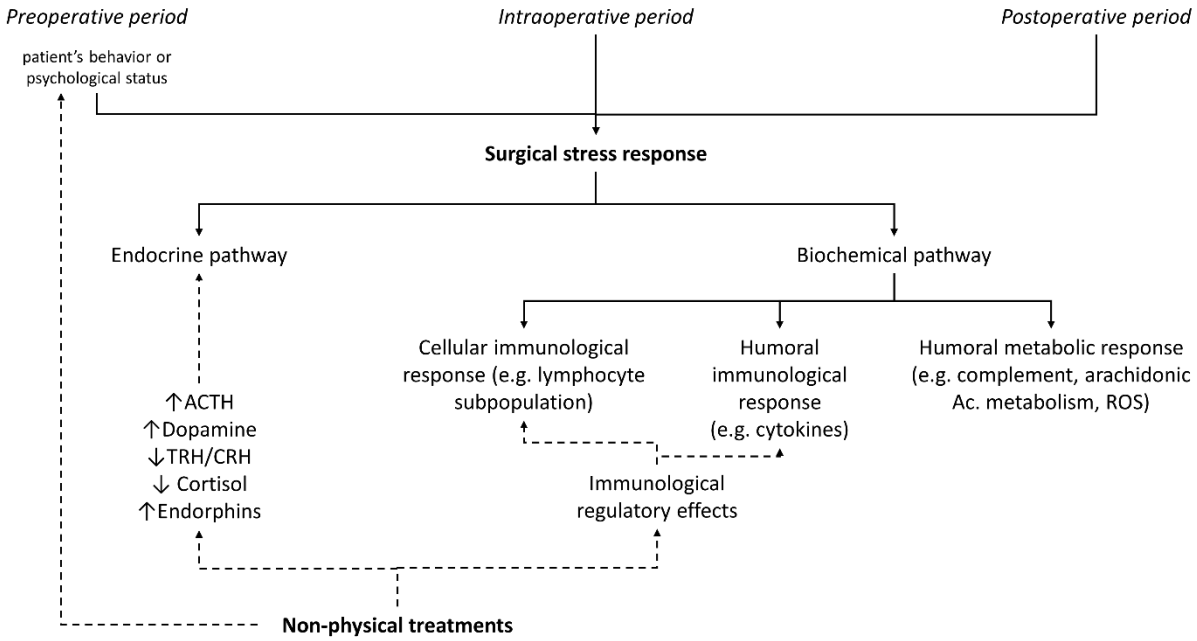

Fig 2. Effects of non-physical treatments on the surgical stress response.

In particular, psychological interventions have been demonstrated to positively interact with the surgical stress response. Through the management of physical or emotional distress, these treatments have proved effective in reducing length of stay in hospitals, pharmacological treatment requirements, and perioperative symptoms such as pain and anxiety (Salmon 1992). In a randomized controlled trial with obese patients undergoing knee arthroplasty, Huebner et al. found that patients receiving a 24-week cognitive behavioral intervention had lower levels of osteoarthritis-related inflammatory markers, suggesting that the inflammatory state can be successfully modulated with psychological interventions (Huebner et al. 2016). Similarly, Thornton et al. randomized 45 patients with clinically significant depressive symptoms and recent diagnosis of breast cancer to receive psychological interventions (Thornton et al. 2009). The authors observed a significant reduction in depressive symptoms, pain, fatigue, and improvement in markers of systemic inflammation (e.g. CD3+, CD4+, CD8+, CD56+ lymphocytes, neutrophil count, and the helper suppressor ratio CD4+/CD8+T cells). Interestingly, they also found reduced depressive symptoms to be a consequence of intervention-related immune changes. The authors concluded that psychological treatments directly reduced

depressive symptoms and indirectly reduced inflammation while effectively treating fatigue and pain (Thornton et al. 2009). Currently, several observational or interventional studies consistently describe the effects that psychological interventions have on the neuroendocrine and inflammatory responses to surgical stress (Antoni et al. 2009; Lengacher et al. 2019; Witek-Janusek et al. 2008). Interestingly, most of these studies show that biochemical effects are associated with improved surgical outcomes. Powell et al. conducted a meta-analysis and reviewed the effects of psychological treatments on postoperative outcomes in adult patients undergoing elective surgery under general anesthesia (Powell et al. 2016). By examining data on 10,302 patients from 105 randomized clinical trials, the authors concluded that psychological treatments are unlikely to be harmful and may positively improve postoperative pain, behavioral recovery, negative affect, and length of stay. Nonetheless, evidence was deemed insufficient to define the exact role of psychological preparation in perioperative care (Powell et al. 2016).

Generally speaking, cognitive-behavioral interventions and narrative medicine have both been identified as effective preoperative approaches capable of improving surgical stress response and outcomes.

2.4.1 Cognitive-Behavioural Therapy (CBT)

Patients' negative beliefs, thoughts, and expectations may lead to a maladaptive response to surgical stress. In particular, fear-avoidance beliefs, catastrophic thinking, feelings of helplessness, and lack of control seem to be associated with passive coping strategies like rest and avoidance behaviors. According to the fear-avoidance model, catastrophic thinking is a prerequisite and a core element for the development of avoidance behaviors (Pincus et al. 2006). The model suggests that individuals experiencing negative beliefs will have a perception imbued with catastrophic interpretations. In an attempt to avoid the perceived catastrophic threat, patients engage themselves in avoidance behaviors and gradually become more disabled and deconditioned. As a result, patients refrain from an increasingly larger array of movements and activities, and may spend a lot of time resting. These maladaptive coping behaviors may delay, or even obstruct, rehabilitation after surgery and increase the rate of postoperative complications. In the course of time, patients may become increasingly more disabled and limited in their work and social life, with consequent impairment of their quality of life.

Within these premises, the aim of cognitive behavioral therapy (CBT) is to identify

and challenge maladaptive thoughts by positively modifying feelings and behaviors, and thereby the experience of "surgery" as a whole (Rolving et al. 2014): interventions may focus on the cognitive component or directly influence behavioral responses. In the medical context, the biopsychosocial approach of CBT focuses on the complex interplay of cognitive, behavioral, emotional, and social factors, and how they interact with biomedical factors (Rolving et al. 2014). The basic assumption is that characteristics such as preoperative anxiety, fear-avoidance beliefs, maladaptive coping strategies, and pain catastrophizing may predict more severe pain, reduced function, frequent postoperative complications, and poorer quality of life after surgery (Rolving et al. 2014). The strong relationship between attitudes and behaviors has been shown in several studies focusing on patients suffering with chronic low back pain (Walsh and Radcliffe 2002). Interventions involving CBT to target catastrophizing and fear-avoidance behaviors have been associated with reduction in physical disability, depression, and postoperative complications (Abbott, Tyni-Lenné, and Hedlund 2010; Fairbank et al. 2005; Griffiths et al. 2010; Moore 2010; Walsh and Radcliffe 2002). Besides having positive effects on postoperative behaviors, moods, pain and physical rehabilitation, CBT has been demonstrated to reduce postoperative complications through direct interaction with the neuroendocrine pathways typically observed during maladaptive surgical stress response and outlined in the previous section. Some examples are described below.

Relaxation interventions

Relaxation techniques include physical and cognitive treatments, such as simple or progressive muscle relaxation and breathing practices, aimed at reducing sympathetic arousal, increasing the feeling of calm, and improving control of postoperative pain (LaMontagne et al. 2003). In a prospective randomized controlled trial, La Montagne et al. demonstrated a positive effect of these techniques on adolescents undergoing major orthopedic surgery; in particular, relaxation interventions were statistically correlated with reduction in pain, anxiety, and postoperative complications (LaMontagne et al. 2003). Similar results were found in a more recent randomized controlled trial showing that relaxation therapy, in addition to analgesic, was effective in reducing postoperative pain with no increase in side effects (Good et al. 2010). Relaxation interventions have also proved effective in reducing emotional distress, improving healthy behaviors, and enhancing immune responses in women treated for breast cancer (Andersen et al.

2004). In a study by Andersen et al., breast cancer patients received relaxation therapy to reduce stress as well as interventions aimed at improving mood, altering unhealthy behaviors, and maintaining adherence to cancer treatment. Patients in the intervention group showed significant reduction in anxiety compared to the control group. Interestingly, the immune response of patients in the intervention group was consistent with psychological and behavioral improvements; in particular, in-vitro stimulation of T-cell proliferation increased in these patients (Andersen et al. 2004).

Mindfulness-Based Interventions (MBI)

MBIs can be considered as psychological interventions inspired by spiritual/religion-based practices of meditation and contemplation, nowadays rapidly emerging as effective techniques in health care settings. Like other psychological interventions, MBIs have proved effective in reducing the physical and psychological symptoms of stress (Lewis 2016). MBIs presuppose patient engagement with the relevant aspects of the present experience in a non-judgmental way: the patient is trained to suspend judgment and to divert explicit attention from a priori beliefs and other regulative representations in order to fully experience the present inner responses to contingency and emotions. This attitude enhances the development of a greater feeling of emotional balance and well-being (Kaplan, Goldenberg, and Galvin-Nadeau 1993). Mindfulness usually requires a systematic mindfulness-based stress reduction (MBSR) program that includes sitting meditation, group discussions, didactics, and home practice on topics including perceptions and reactions to events in life (Hoffman et al. 2012). MBSR has been shown to improve long-term conditions such as pain (Kabat-Zinn, Lipworth, and Burney 1986), anxiety (Miller, Fletcher, and Kabat-Zinn 1995), and other psychological symptoms (Astin 1997).

Written emotional disclosure

Emotional disclosure is a psychological technique that encourages patients to write, in as much detail as possible, about their feelings and emotions related to stress experiences and/or previous traumatic events (Meads and Nouwen 2005). Similar to other preoperative CBT interventions, written emotional disclosure may be useful in reducing stress and enhancing physical and psychological health in the perioperative period, thus improving surgical outcomes and reducing length of hospital stay (Johnston and Vögele 1993; Montgomery, David, and Winkel 2002).
Disclosure of traumatic experiences was statistically correlated with reduction in

postoperative complications, mainly through upregulation of the immune function (Weinman, Ebrecht, and Scott 2008), and more effective wound healing (Weinman, Ebrecht, and Scott 2008). In a prospective controlled study, Weinman et al. investigated the impact of disclosure interventions on the progress of wound healing after punch biopsy. Patients enrolled in the experimental (emotional disclosure) group had to prepare a written report on previous traumatic and distressing experiences, paying particular attention to emotions and feelings related to these events. On the other hand, patients in the control group were asked to write about time management, trying to be as objective as possible, paying attention to details and neglecting emotions. The authors observed that patients in the experimental group experienced significant reduction in postoperative complications and more rapid wound healing than those in the control group (Weinman, Ebrecht, and Scott 2008).

2.4.2 Narrative Medicine

Narrative medicine can be defined as a medical approach acknowledging the value of people's narratives and individual stories, focusing on the relational and psychological dimensions that are involved in physical illness. According to Lewis, "even the most rigorous medical science contains human perspectives, interests, and goals imbedded in the way knowledge is selected, organized and prioritized" (Lewis 2016). Over the last two decades, clinical practice fortified by narrative competence has been largely adopted as a model for humane and effective medical practice (Griffiths et al. 2010).

The narrative aspect of medicine had already been recognized by Hippocrates, according to whom 'the sort of disease a person has is much less important than the sort of person that has the disease'. In fact, one of the primary ways in which humans encounter themselves and each other and deal with illness and suffering is through storytelling, that is, the process of framing one's experience as a narrative that is imbued with subjective thoughts, feelings, and meaning. Therefore, in order to effectively support patients, healthcare professionals must participate in this process and experience the story of their patients' illness by creating a meaningful and personal connection (Mahr 2015). Surgical patients are neither their symptoms nor their diagnoses: patients are persons who face their diseases with expectations, fears, and hopes. The same principle holds true for any phase of illness and care. In conclusion, it is plausible to hypothesize that narrative medicine could enhance

stress resilience in patients in the perioperative period. Nonetheless, at present – and to our knowledge – no studies are available in the literature that evaluate the direct impact of a narrative medicine approach on surgical outcomes and surgical stress response.

2.5 Effects of psychological interventions on anxiety and pain in patients undergoing major elective abdominal surgery

The large number of systematic reviews and meta-analyses focusing on the effects of psychological interventions on surgical outcomes in breast, cardiac or orthopedic surgery patients suggest this kind of approaches be most frequently applied in these specific settings (Richards et al. 2017; Szeverenyi et al. 2018). In other surgical specialties (even abdominal surgery, which includes some of the most common surgical procedures worldwide), a less systematic approach to evaluation of the influence of psychological interventions on surgical outcomes seems to have been adopted. With these concepts in mind, here we analyze the effects of the most common psychological interventions on surgical pain and/or anxiety in adult patients scheduled for elective general abdominal surgery.

We carried out a review taking into consideration only prospective, controlled clinical trials and observational studies involving psychological interventions in adult patients scheduled for elective general abdominal and/or urologic surgery. Only studies published in English from January 2000 to December 2019 reporting pain and/or anxiety among outcome measures were considered. The analysis has been confined to those psychological interventions considered to be realistically applicable during perioperative management of abdominal surgery patients. Specifically, the following psychological techniques were considered: 1) Relaxation techniques, 2) Mindfulness, 3) Cognitive-Behavioral Therapies, 4) Narrative Medicine, 5) Hypnosis, 6) Coping strategies.

In this review, we outline the effects of perioperative psychological interventions (such as Cognitive-Behavioral Therapies, Relaxation techniques, Mindfulness-based interventions, Hypnosis, Coping strategies, and Narrative Medicine) on surgical pain and/or anxiety in adult patients scheduled for elective general abdominal and/or urologic surgery. Several studies suggest that psychologic/psychosocial, preoperative patient factors directly interact with the pathophysiological mechanisms underlying the surgical stress response (Mavros et

al. 2011), potentially affecting wound repair, innate and adaptive immunity, inflammation, perception of pain, and mood. Here we describe how psychological interventions can influence pain and/or anxiety in abdominal surgery patients through interaction with the pathophysiological mechanisms involved in the neuroendocrine and inflammatory response to surgical stress.

Acute and/or chronic stress, including surgery-related perioperative stress, has been shown to extensively affect patients' neuroendocrine pathways (Maduka, Neboh, and Ufelle 2015). Interestingly, there is evidence to suggest that psychological interventions might modulate perioperative neuroendocrine homeostasis in patients undergoing abdominal surgery (Manyande et al. 1995). On this basis, considering in particular the neuroendocrine effects on endogenous opioid response and gate control system, Roykulcharoen and colleagues designed a randomized controlled trial aimed at demonstrating the positive effect of systematic relaxation on postoperative pain in abdominal surgical patients (Roykulcharoen, Good, and Bolton 2004). Based on subjective (based on VAS scores) and objective (based on 6-hours opioid intake) assessment of pain, the authors found that patients randomized to relaxation therapy experienced less postoperative pain (Roykulcharoen, Good, and Bolton 2004). Using a similar approach, Good and colleagues investigated the effects of relaxation therapy in a randomized controlled trial with 517 abdominal surgery patients (Good et al. 2010). The rationale for this study is the ability of relaxation techniques to promote a natural analgesic effect via increased parasympathetic activity and endogenous inhibitory mechanisms. In this study, psychological treatments were associated with a 25% reduction in VAS scores postoperatively (Good et al. 2010).

In line with the results obtained by the above mentioned studies, most of the psychological treatments examined in this review seem to contribute to increase the secretion of inhibiting hypothalamic hormones, such as somatostatin or dopamine, and decrease the secretion of releasing hormones, such as thyrotropin- and corticotropin-releasing hormones and the growth hormone-releasing factor (Jindal, Gupta, and Das 2013). As a consequence, cortisol levels decrease (Walton et al. 1995) whereas levels of beta-endorphins may increase (Jindal, Gupta, and Das 2013). All these factors may contribute to improve pain experience and reduce anxiety associated with abdominal surgical procedures. Manyande and colleagues designed a controlled trial involving 51 patients undergoing general abdominal surgery to test the capability of relaxation interventions and guided imagery to increase the ability to cope with surgical stress. This study demonstrated that patients

in the interventions group had less severe pain and less frequent postoperative complications than those in the control group. In addition, cortisol levels assessed immediately before and after surgery were lower in patients receiving psychological treatments (Manyande et al. 1995).

Psychologic/psychosocial patient factors have been shown to interact with perioperative inflammation (e.g. cytokine expression (Broadbent et al. 2003)), and consequently with wound repair (Glaser et al. 1999) and pain perception. On this basis, considering in particular the effects of psychological stress on leptin resistance, neuropeptide Y and inflammatory cytokines, Sockalingam and colleagues designed an observational prospective pre/post study aimed at demonstrating the positive effect of perioperative cognitive behavioral therapy in a group of abdominal surgery obese patients undergoing bariatric surgery (Sockalingam et al. 2019). The authors demonstrated this type of psychological therapy had a positive effect on postoperative depressive symptoms, anxiety, and eating psychopathology (Sockalingam et al. 2019). In an observational study, Glaser and colleagues correlated the symptoms of psychological stress with an ineffective regulatory pattern for IL-1 and IL-8 production in the wound site (Glaser et al. 1999). Similar results were obtained in an observational study of 47 adult patients undergoing surgical repair of inguinal hernia (Broadbent et al. 2003). The authors described the relationship between wound healing and psychological stress through the tissue levels of IL-1, IL-6, and matrix metalloproteinase-9. In the same study, preoperative psychological stress significantly predicted low levels of IL-1 and matrix metalloproteinase-9 in the surgical wound, as well as severe pain, postoperative complications and poor and slow recovery ((Broadbent et al. 2003)). The same authors obtained consistent results in a trial with 60 patients undergoing videolaparoscopic cholecystectomy randomized to treatment with relaxation therapies (Broadbent et al. 2003). Specifically, a greater reduction in anxiety and perceived stress was observed in the relaxation group compared with the control group, from pre-intervention to 7-day follow-up ($p<0.05$). Interestingly, the authors observed that patients treated with perioperative relaxation interventions had higher hydroxyproline deposition in the wound (i.e. expression of tissue repair) than those in the control group (difference in means 0.35, $p = 0.03$).

The interactions between psychological treatments and pathophysiology of surgical stress response might explain why these treatments have been associated with reduction of perioperative anxiety, pain, and pharmacological treatment requirements.

Hizli and colleagues designed a randomized controlled trial including 64 patients scheduled for transrectal ultrasound-guided prostate needle biopsy to explore the effects of hypnosis on pain and anxiety. Patients were randomized to receive a 10 min presurgery hypnosis session involving suggestions for increased relaxation and decreased anxiety. Postintervention, and before surgery, patients in the hypnosis group had significantly lower mean values of pain and anxiety, measured using visual analogic scales, Beck Anxiety Inventory, and Hamilton Anxiety Scale, respectively (Hızlı et al. 2015). Similar results were found by Lin and colleagues in a randomized controlled trial involving 62 patients scheduled for abdominal surgical procedures. The authors found that preoperative coping procedures, such as nursing intervention for pain, had positive effects on preoperative pain and anxiety, preoperative pain attitude, and perception of pain (Lin and Wang 2005).

Interestingly, most of the studies discussed in this review mainly relied on subjective measures of pain, such as the visual-analogic or the numeric rating scales. Only two studies (Rejeh et al. 2013; Roykulcharoen, Good, and Bolton 2004) assessed the effects of psychological interventions on perioperative pain through objective measurements, e.g. analgesic requirements. Although both studies show consistent results on the effects of psychological therapies in reducing analgesic requirements, only in the randomized controlled trial by Rejeh et al. were these effects statistically significant (Rejeh et al. 2013).

Results from this review are in agreement with those obtained from studies involving orthopedic or cardiac surgery patients. In particular, in a systematic review of 62 relevant studies published from January 1980 to September 2016, Szeverenyi and colleagues observed that psychosocial interventions significantly reduced postoperative pain (Hedges'g = 0.31 [95%CI = 0.14, 0.48]), and pre- and postoperative anxiety (g = 0.26 [0.11, 0.42] and g = 0.4 [0.21, 0.59], respectively), while no significant effects were associated to postoperative analgesic use (g = 0.16 [95%CI = 0.01, 0.32]. Similar findings were found by Rees and colleagues in a metanalysis exploring the effects of psychological treatments in patients with coronary artery diseases undergoing cardiac surgery. Analyzing results from 36 trials including 12,841 patients, the authors demonstrated a perioperative reduction in anxiety and depression. Notably, both studies included a higher number of studies compared with our review. That can be explained considering both the different temporal limits used for literature search and the historical interest among physicians in reducing symptoms related to the most painful surgical procedures, associated with a high incidence of severe postoperative pain and anxiety (e.g.

orthopedic surgery) or to conditions where anxiety and stress may affect patients' outcomes (e.g. cardiac surgery). Furthermore, differently from what was observed by Szeverenyi and colleagues, we observed a reduction in postoperative pain as well as a reduction in postoperative analgesic use in patients receiving psychological therapies.

The following limitations should be acknowledged. First, studies were limited to English language. Second, in one of the selected studies the effects of perioperative psychological interventions were studied in a cohort of bariatric patients. This population present with peculiar psychological features that usually differ from those observed in the majority of abdominal and/or urologic surgical patients, thus potentially limiting the generalization of the results. Third, in most studies perioperative pain was assessed through subjective scales (e.g. VAS or NRS). More objective indicators of intervention success (e.g. analgesic requirements) were used only in two of the identified studies.

Finally, the treatments explored and the outcomes observed in this brief review differ among the selected studies. For these reasons, a synthesis of the evidence on effectiveness of psychological treatments in reducing perioperative anxiety and pain has not been provided. Nevertheless, the results discussed here seem to suggest a positive effect on anxiety and pain, that certainly merits further investigation in the abdominal/urologic setting.

III Management of Surgical stress and postoperative pain: pharmacological interventions

The interaction with the central nervous system (CNS) is the most known mechanism associated with clinical effects of sedatives. Nevertheless, the interactions between sedatives and other organs and systems are misleading and clinical effects of sedatives, other than sedation, are often underappreciated(Sanders, Hussell, and Maze 2011). Among these, sedative-induced immunomodulation is certainly one of the most important, mainly because immune response is intrinsically involved in acute and chronic critical illness mechanisms. The connection between sedation and immunological impairment has been widely considered as merely theoretical for a long period, and often neglected during routine clinical practice. However, evidence provided over the last ten years have renewed interest in this area(Sanders, Hussell, and

Maze 2011). Nowadays, the immunomodulatory effects of sedation have been demonstrated to influence the clinical course of preexisting inflammatory processes, such as acute respiratory distress syndrome(Matute-Bello, Frevert, and Martin 2008), acute kidney disease(Wan et al. 2008), and delirium(Macdonald et al. 2007), as well as cross-talk with other processes, including the coagulation cascade(Sanders, Hussell, and Maze 2011). Due to the high prevalence of sedative and analgesic use in critically ill patients, the physician should be aware of the sedative effects on the immune response. The aim of this chapter is to analyze the known effects of sedatives on the innate and adaptive immune systems.

3.1 The innate and adaptive immunological systems

The immunological system is a complicated balance of effectors belonging to the innate and adaptive systems.

Innate immunity encompasses a broad range of host defenses, producing an initial non-specific, stereotype and unselective response to a stressful event (either microbiological or not). It is entirely unchanged during evolution and among different species and comprehends barriers, complement, cytokines, phagocytes and other presenting antigen cells, cytotoxic and cytotoxic cells(Sanders, Hussell, and Maze 2011). Circulating molecules, such as complement and cytokines proteins, promote direct and indirect effects on immune system. The former stimulate an amplifying cascade to produce opsonization and lysis of bacteria, chemotaxis of immune effectors, mast cell activation, coagulation, and inflammatory responses by the classic and alternative pathways(Sanders, Hussell, and Maze 2011). The complement end product, the membrane attack complex, damages the cell membrane to facilitate the pathogen osmotic lysis. On the other hand, pro- and anti-inflammatory cytokines coordinate the responses of different immune effectors, through paracrine and autocrine effects(Sanders, Hussell, and Maze 2011). With the aim of presenting non-physiologic and non-self molecules, many different immunologic cells express pathogen recognition receptors (PRR, e.g. Toll-like receptors). The recognition of pathogen-associated molecular pattern (PAMP) receptors and damage-associated molecular pattern (DAMP) by PRR activates other effectors of innate immune system as well as promotes activation of the adaptive immune system. Considering the overlap existing in biological mechanisms stimulated by PAMPs and DAMP, the activation of innate immune system through PRR is similar during infection or trauma(Sanders, Hussell, and

Maze 2011). Phagocytes (mainly macrophages and neutrophils) and other antigen-presenting cells (e.g. dendritic cells) become activated early in this response, migrate (by chemotaxis) to the infected/damaged site, present PAMP/DAMP and produce an inflammatory milieu promoting and coordinating other effectors of the immune system. The generation of reactive oxygen species (by way of a respiratory burst) is a central killing mechanism of macrophages, neutrophils and all other cytotoxic cells(Sanders, Hussell, and Maze 2011).

Adaptive (or acquired) immune system is phylogenetically more recent, being presented only in vertebrates. It comprehends a humoral and cellular component and differs from innate immune system for the specific and memory-producing responses(Sanders, Hussell, and Maze 2011). The proliferation of antibody-secreting plasma cells from specific antigen-stimulated B lymphocytes sustains the humoral component of the adaptive immune system, while T lymphocytes (i.e. helper, cytotoxic and regulatory T cells) the cellular component. Among T cells, Th lymphocytes secrete cytokines, elaborate and prime the immune response, inducing immunoglobin class switching of B cells, activation of cytotoxic T (Tc) cells and optimizing the bactericidal activity of phagocytes(Sanders, Hussell, and Maze 2011). Th lymphocytes, characterized by expression of CD4 proteins, are activated when the MHC type II molecules expressed on antigen-presenting cells bind the specific T cell receptor. Th1 cells are regarded as "pro-inflammatory," secreting cytokines (e.g. interferon-γ and interleukin (IL)-12) and stimulating macrophage and cytotoxic T cell functions. Th2 cells secrete cytokines (e.g. IL-4 and IL-10) and have been associated with an "anti-inflammatory" phenotype. Th cells also comprehend the regulatory T cells (Treg) (that act to dampen the immune response) and the Th17 cells (that modulates neutrophil function)(Sanders, Hussell, and Maze 2011). A shift from Th1 to Th2 cells (i.e. mainly induced by deregulated lymphocytes apoptosis) has been observed in the tardive stages of sepsis; the subsequent anti-inflammatory/immunosuppressive phenotype has been associated with secondary infections and death in septic patients(Hotchkiss and Nicholson 2006). Tc cells can induce death in somatic or tumor cells, after stimulation by MHC type I-related signaling, through the release of cytotoxins, perforin and granulysin, the subsequent pores formation in the target cell membrane, the entrance of serine proteases and thus the induction of apoptosis. Alternatively, Tc expression of Fas ligand can activate the extrinsic apoptotic cascade, inducing cell death(Sanders, Hussell, and Maze 2011).

3.2 Effects of sedative on immune responses

Most of the studies aimed at exploring the immunomodulatory effects associated with sedatives are unfortunately performed in a setting of the operating room. For this reason, most of the results presented in this review are mainly derived from clinical studies in which sedatives are used at hypnotic doses during general anesthesia.

Although only preliminary results are available, most of the studies aimed at exploring the immunomodulatory effects of sedatives suggest a predominant anti-inflammatory pattern associated with these agents, as well as an increased susceptibility to infection. α2-adrenoceptor agonists might be a possible exception to this generalization; indeed, these might be associated with an improved immune function and better outcomes, even in septic patients(Sanders, Hussell, and Maze 2011).

Several pathophysiological reasons might explain the effects of different sedatives. As example, as sleep deprivation may contribute to the immune dysfunction in critically ill patients(Vincent et al. 2016), the sedative profile of the different agents may consistently have an immunomodulatory effect. Different from gabaergic agents (e.g. propofol or benzodiazepine) and opioids, which reduce the amount of non-rapid eye movement sleep, dexmedetomidine is associated with electroencephalographic and cerebral blood flow patterns similar to natural sleep(L. E. Nelson et al. 2003; Sanders and Maze 2007). The improvement on the burden of sleep deprivation might explain the more favorable immune effect of dexmedetomidine in the ICU than other sedatives(Sanders, Hussell, and Maze 2011).

Another general indirect effect of sedatives on immune system might derive from the stimulation of autonomic nervous system induced by different sedatives. In particular, the activation of the sympathetic nervous system (SNS) has been associated with immune dysfunction(Nance and Sanders 2007; Smith et al. 1977). In this context, the suppression of SNS activity by sympatholytic sedation (e.g. α2-adrenoceptor agonist) may exert some advantages to the immunological system(Sanders, Hussell, and Maze 2011). Consistently, the sympathomimetic effects associated with ketamine use are associated with a profound immunosuppression(Beilin et al. 2007). In particular, sedative doses of ketamine affect the immunoregulatory activities of macrophages, neutrophils and mast

cells(Ohta, Ohashi, and Fujino 2009). Furthermore, Ohta et al have demonstrated that ketamine inhibits the dendridic cells production of IL-12 and the T cells differentiation(Ohta, Ohashi, and Fujino 2009). Finally, even a single preoperative administration of ketamine has been demonstrated enough to attenuate the production of pro-inflammatory cytokines from peripheral blood mononuclear cells and the proliferative response of mononuclear cells(Beilin et al. 2007; Ohta, Ohashi, and Fujino 2009). However, as ketamine is rarely used for long term sedation in the ICU, it will be not extensively discussed in this review.
Beyond these general mechanisms, different effects on the immune system have been demonstrated for each specific sedative agent.

3.3 Propofol

Propofol and midazolam have been probably the most common sedatives used for critical care sedation for an extended period of time(Kelbel and Weiss 2001). Both exhibit natural anti-inflammatory/immunosuppressive effects in several in-vitro and in-vivo models and, if used for long-term sedation in critically ill patients, have been associated with a clinically relevant impairment of the immune response(Kelbel and Weiss 2001). As example, four hours sedation with propofol may lead to reticuloendothelial system dysfunction, enhancing lung and spleen bacterial colonization in an animal model of infection(Kelbel et al. 1999). Probably, the intralipid-based formulation may contribute to propofol-induced immunosoppression(Heine et al. 1996; Kelbel and Weiss 2001). All these effects are partially sustained by the propofol inhibition of macrophage and neutrophil functions; furthermore, it exhibits antioxidant properties both inhibiting in-vitro generation of reactive oxygen species(Heine et al. 1996; Mikawa et al. 1998), and reducing in-vivo free radical generation in cardiac surgery in humans(Corcoran et al. 2006). This antioxidant effect may contribute to the in-vitro observation of neutrophil phagocytosis impairment for Escherichia Coli and Staphylococcus Aureus(Heller et al. 1998; Krumholz, Endrass, and Hempelmann 1994). This in-vitro effect might be due to a reduced intracellular calcium concentration in neutrophils(Mikawa et al. 1998). Interestingly, this phagocytosis impairment seems to be similar to that induced from other sedatives. In particular, ex-vivo studies have observed no effects on propofol-induced impairment on S. Aureus phagocytosis, both during sedation (compared with methohexital(Huettemann et al. 2006)) and anesthesia (compared with isofluorane(Heine et al. 2000)). Finally, a

reduced hydrogen peroxide production from septic rat ex-vivo neutrophils was also observed with propofol(Inada et al. 2001), as well as suppression of LPS-induced release of the chemotactic and activating factor IL-8 from isolated neutrophils(Galley, Dubbels, and Webster 1998).

Impairment on macrophage chemotaxis, oxidative burst, and phagocytosis of E. coli have thus all been reported during propofol administration(Chen, Wu, Chang, et al. 2003; Heller et al. 1998); these effects may be related to the loss of mitochondrial membrane potential and reduction in macrophage ATP levels(Chen, Wu, Chang, et al. 2003). Furthermore, as propofol inhibits inducible nitric oxide synthase (iNOS)(Chang et al. 2002; Chen et al. 2005; Chen, Wu, Tai, et al. 2003), it suppresses lipopolysaccharide (LPS)-induced nitric oxide formation(Chang et al. 2002; Chen et al. 2005; Chen, Wu, Tai, et al. 2003) as well as nitric oxide-induced apoptosis in macrophages(Chang et al. 2002).

Although data at sedative dose are missing, propofol seems to preserve Th1/Th2 lymphocyte subsets at anesthetics dose(Inada et al. 2004). Nevertheless, ex-vivo studies suggest that propofol might entirely reduce proliferative lymphocyte responses in critically ill patients(Pirttikangas et al. 1995). In particular, it can inhibit lymphocyte potassium channels, attenuating lymphocyte activation and proliferation(Mozrzymas, Teisseyre, and Vittur 1996). Furthermore, propofol may induce lymphocyte apoptosis, but at high concentrations (beyond sedative purpose)(Song and Jeong 2004).

Systemically, low-dose propofol attenuates the plasma increase of TNFα and IL-6 levels when given immediately or 1 or 2 hours after endotoxin administration(T Taniguchi et al. 2000; Takumi Taniguchi, Kanakura, and Yamamoto 2002). Interestingly, the lowest was the dose of propofol administered, the lowest was the cytokine attenuation observed. Although this effect might be generalizable for propofol sedation, most of the studies aimed at quantifying circulating inflammatory mediators reduction have never been tested at doses below 5 mg/kg/h(Hsu et al. 2005). Critically, at high doses (20 mg/kg/h) propofol impairs bacterial clearance from the lung and spleen in rabbits injected with E. Coli in-vivo (compared with ketamine)(Kelbel et al. 1999).

As a conclusion, although most of the data available on propofol-based sedation are only derived from anesthesia and surgical settings, significant in-vitro and in-vivo data suggest that propofol has anti-inflammatory effects due to impairment of the innate immune response. Scarce information are available on functional

effects of propofol on the adaptive immune response. Propofol may have a therapeutic application for attenuation of sterile inflammation; however, in the presence of infection, the impaired bacteria clearance may prove a significant problem.

3.4 Benzodiazepines

Similar to propofol, benzodiazepines are often used for critical care sedation and present an immune-suppressant profile(Sanders, Hussell, and Maze 2011). Nevertheless, slight differences might be observed between these sedatives in several in-vivo studies. In particular, forty-eight hours of midazolam infusion have been associated with a more profound reduction of serum pro-inflammatory cytokine (IL-1b, IL-6 and TNFα) than propofol infusion in critically ill patients(Helmy and Al-Attiyah 2001). Furthermore, serum concentrations of IL-8 (i.e. neutrophil chemotactic factor, an important mediator of the immune reaction in the innate immune system response) decreased more pronouncedly in the midazolam group. Finally, the reduction in IL-2-serum concentrations and the increase in interferon-gamma levels were more relevant in the propofol group(Helmy and Al-Attiyah 2001). Thus, clinical data on critically ill patients support a greater anti-inflammatory/immunosuppressant potential for midazolam than for propofol.

In preclinical studies performed on animal models, the benzodiazepines' anti-inflammatory actions mainly involve the innate immune and correlate with increasing mortality due to infections. As example, midazolam significantly inhibits LPS-induced up-regulation of cyclooxygenase 2, inducible nitric oxide synthase in macrophages, NF-kB transcriptional activity, protein kinase, and superoxide production(Kim et al. 2006). An impairment in macrophages oxidative burst and bacterial phagocytosis have also been demonstrated with midazolam in preclinical studies(Massoco and Palermo-Neto 2003). Finally, benzodiazepines suppress LPS-induced TNFα activity in macrophages(Matsumoto et al. 1994).

Conflicting results exist on benzodiazepine effects on neutrophils function; in particular, whereas some evidence suggests a neutrophils impairment induced by midazolam(Massoco and Palermo-Neto 2003), an acute dose of diazepam seems to correlate with a pro-inflammatory effect, improving neutrophil function. Nevertheless, chronic diazepam assumption correlates with an immune depressant effect(Galdiero et al. 1995; da Silva et al. 2003) with depression of

polymorphonuclear cell phagocytosis, adherence, and chemotaxis(da Silva et al. 2003). Further in-vitro studies suggest that benzodiazepines suppress neutrophil oxidative burst(Finnerty et al. 1991; Muhling et al. 2001; Weiss et al. 1993); this effect was thus blocked by the peripheral benzodiazepine receptor antagonist PK 11195(Matsumoto et al. 1994).

Only preliminary results are available for benzodiazepine effects on lymphocytes functions. In particular, evidence from animal studies suggests that low-dose of benzodiazepines improves stimulated lymphocyte proliferation over the first weeks of treatment; whereas with longer treatment times a decreased lymphocyte proliferation is observed, until to impaired lymphocyte humoral responses following long-term (60 days or greater) treatment(Galdiero et al. 1995).

Preliminary data show that low-dose benzodiazepines impair Salmonella Typhimurium clearance and, particularly for long-lasting treatment, increases mortality from this infection(Galdiero et al. 1995). Furthermore, an in-vivo study showed that, even with short term treatment, benzodiazepines reduce resistance to systemic Klebsiella Pneumoniae, increasing mortality(Laschi et al. 1983). Similarly, epidemiologic data have reported benzodiazepine use as a risk factor for complicated community-acquired lower respiratory tract infection(Hak et al. 2005).

As a conclusion, similar to propofol, benzodiazepines induce suppression of innate immune response probably through peripheral benzodiazepine receptor on immune cells(Decaudin 2004). An increased mortality rate due to infection correlates with impairment of the innate immune response; on the other hand, studies probing effects on adaptive immunity are needed.

3.5. Opioids

Opioids are often used for critical care sedation to facilitate mechanical ventilation and improve the patient's comfort(Sanders, Hussell, and Maze 2011). Several pieces of evidence suggest that opioids suppres innate and adaptive immune systems(Sabita Roy et al. 2006; Vallejo, de Leon-Casasola, and Benyamin 2004). Nevertheless, most of the studies on this specific topic are focused on morphine use, and only few data are currently available on the suppressing effects of other opioids(Sanders, Hussell, and Maze 2011).

Morphine has been associated with in-vitro anti-inflammatory effects; consistently, an increased mortality rate has been observed in several in-vivo

animal models of infection(Weinert, Kethireddy, and Roy 2008). In particular, morphine treatment was associated with worst outcome during Streptococcus Pneumoniae(Jinghua Wang et al. 2005, 2008), Salmonella Typhimurium(MacFarlane et al. 2000), Salmonella Enterica(Asakura et al. 2002; Feng et al. 2006), Toxoplasma Gondii(Chao et al. 1990) or Listeria Monocytogenes infections(Asakura et al. 2006). Furthermore, animals chronically treated with morphine spontaneously developed infections with enteric bacteria, suggesting that opioid treatment may contribute to the translocation of gram-negative bacteria also in critically ill patients(Hilburger et al. 1997).

These effects might be correlated with morphine-induced inhibition of myeloid cell differentiation(Tian et al. 1997) and, generally, with the overall suppression of immune responses at the early stage of activation. In particular, morphine inhibits phagocytosis and macrophage activation(Szabo et al. 1993; Tomassini et al. 2004), chemotaxis(Choi et al. 1999; Miyagi et al. 2000) and cytokine expression(Bhat et al. 2004). Furthermore, several studies suggest an opioid-induced inhibition of macrophage respiratory burst activity(Stefano et al. 2001; Jinghua Wang et al. 2002) and induction of superoxide and NO formation(Bhat et al. 2004; P. C. Singhal et al. 2002), leading to inappropriate macrophage apoptosis(Sanders, Hussell, and Maze 2011).

μ opioid receptors seem to be related to all these effects; indeed, specific μ antagonists reduce morphine's immunological effects, while δ or κ antagonists had no effects(Fecho et al. 1994; Pacifici et al. 1995; Szabo et al. 1993). Furthermore, μ opioid receptor gene deletion reduces opioids-related phagocytosis impairment(S Roy et al. 2001; S Roy, Barke, and Loh 1998). On the other hand, the anti-inflammatory effect leading to reduced TNFα, IL-1, and IL-6 production may involve μ as well as other opioid receptors(Sabita Roy et al. 2006). Although μ receptors on the macrophages and lymphocytes surface seem to be related to this effect, exact mechanisms of opioid-induced immune suppression are not completely understood. Nevertheless, increasing evidence suggest also indirect mechanisms for opioid-induced immune suppression involving the stimulation of the hypothalamic-pituitary axis and the SNS(Sabita Roy et al. 2006; Vallejo, de Leon-Casasola, and Benyamin 2004; Weinert, Kethireddy, and Roy 2008). Interestingly, α2-adrenoceptor agonist, such as clonidine, ameliorated the immune effects of morphine withdrawal(West, Dykstra, and Lysle 1999).

Opioids suppress NK cell activity both after acute or chronic administration(Sabita Roy et al. 2006), through an effect probably mediated from a CNS locus. In particular, opioids analogues unable to diffuse across the blood–brain barrier (e.g. N-methyl morphine) do not produce this NK cell activity inhibition(Lysle, Hoffman, and Dykstra 1996).

Chronic opioid treatment reduces proliferation of thymocytes and T lymphocytes and induces an imbalance in the lymphocyte subsets, as well as in their function and apoptosis control(Sanders, Hussell, and Maze 2011). In particular, treatment with morphine and fentanyl inhibits lymphocytes proliferation and increases cellular apoptosis(Flores, Hernandez, and Bayer 1994; J Wang et al. 2001). Similarly to macrophages, lymphocytes seem to be induced to apoptosis through morphine-induced upregulation of Fas and caspase pathways(Bhat et al. 2004; P. Singhal et al. 2001; P. C. Singhal et al. 2002; J Wang et al. 2001; Yin et al. 1999). Several authors suggest that lymphocytes apoptosis might be critical for septic pathogenesis, involving intrinsic and extrinsic apoptotic mechanisms(Hotchkiss and Nicholson 2006) with subsequent caspase activation and sensitization to septic injury. However, it is unclear if these findings might be applicable also in critically ill septic patients in the ICU, particularly taking into consideration timing and dosing of opioids used for sedation in these patients. Most of these authors conclude that further studies focused on clarifying the effects of opioids on sepsis-induced apoptosis are urgently required(Sanders, Hussell, and Maze 2011).

Furthermore, chronic opioids treatment produces a shift from Th1 to Th2 lymphocyte subset, probably through intracellular (e.g. adenylyl-cyclase–mediated differentiation factors(Sabita Roy et al. 2004, 2005)) and humoral mechanisms (e.g. opioids- induced inhibition of Th1 cytokines, IL-2 and IFN-g, and concomitant increase of Th2 cytokines, IL-4 and IL-5 (Avidor-Reiss et al. 1996; Sabita Roy et al. 2005)). Opioids also impair the transition from B cells to plasma cells through an μ opioid receptor-mediated mechanism, further inhibiting the adaptive immune response. Finally, morphine exposure also downregulates MHC class II expression, affecting antigen presentation(Bayer et al. 1990).

As a conclusion, opioid's effects on macrophages and lymphocytes may have a critical importance in the ICU patients, leading to acquired suppression of both innate and adaptive immunosystem. Particularly in critically ill patients, the opioid administration may therefore contribute to the immunosuppression, predisposition to infection and participate in sepsis pathogenesis.

3.6 a2-adrenorepector agonists

The SNS exerts immunosuppressive effects through direct stimulation of α1- and β-adrenoceptors on immune effectors. In particular, these receptors trigger signaling cascades that reduce the expression in the immune cells of pro-inflammatory cytokines increasing those with anti-inflammatory effects(Deng et al. 2004; Sternberg 2006) and contributes to lymphocytes apoptosis(Oberbeck et al. 2004; Stevenson et al. 2001). Interestingly, stimulation of α2-adrenoceptors may induce both a pro-inflammatory(Flierl et al. 2007; Spengler et al. 1990) and anti-inflammatory response(Memis et al. 2007; Nader et al. 2001; Takumi Taniguchi et al. 2004, 2008; Venn et al. 2001), probably depending on the different peripheral and CNS actions of α2-adrenoceptors agonists. Peripherally, α2-adrenoceptors stimulate innate immunity and pro-inflammatory effects(Gets and Monroy 2005; Miles, Lafuse, and Zwilling 1996; Weatherby, Zwilling, and Lafuse 2003), while centrally the sympatholytic actions of α2 agonists may reduce inflammation, shifting towards an anti-inflammatory phenotype(Sternberg 2006; Tracey 2007). Furthermore, inflammation itself may modulate the effect of α2-adrenoceptor stimulation(Sud et al. 2008); as example, dexmedetomidine administered during systemic inflammation may act in an anti- rather than pro-inflammatory manner(Sanders, Hussell, and Maze 2011). As a consequence, a highly modulated pro-/anti- inflammatory responses might be observed during α2-adrenoceptor agonists treatments. As example, in contrast to benzodiazepines and propofol effects, α 2-adrenoceptor agonists increase in-vivo macrophage phagocytosis, free radicals, superoxide and NO-dependent killing of pathogens, such as Mycobacterium Avium and Toxoplasma Gondii(Gets and Monroy 2005; Miles, Lafuse, and Zwilling 1996; Weatherby, Zwilling, and Lafuse 2003). Furthermore, α2-adrenoceptor agonists increase production of pro-inflammatory cytokines(Weatherby, Zwilling, and Lafuse 2003); in particular, a dose-dependent TNFα production is observed in-vitro with α 2-adrenoceptor stimulation(Spengler et al. 1990), as well as an in-vitro IL-12 monocytes production that may stimulate cell-mediated and Th1 immune response(Kang, Lee, and Kim 2003). Nevertheless, these pro-inflammatory effects might be counterpoised to anti-inflammatory effects observed in-vivo in other studies in which dexmedetomidine attenuated ventilator-induced lung injury correlating with reduced local inflammatory responses(Yang, Tsai, and Huang 2008).

At clinical doses, clonidine and dexmedetomidine don't affect chemotaxis, phagocytosis, and superoxide formation in human neutrophils(Nishina et al. 1999). Only few studies have explored the effects of α2-adrenoceptor agonists on lymphocytes. Nevertheless, similarly to other sedatives and the opioids, a significant reduction of Th1 phenotype in T cell subsets has been observed during systemic inflammation(von Dossow et al. 2006). However, a concomitant reduction in T regulatory cells has been also in-vivo observed during sedation with dexmedetomidine. In particular, in a randomized controlled trial on septic patients, Guo et al. concluded that dexmedetomidine might decrease the duration of immune suppression in these patients, through a more rapid normalization of T regulatory cells count than propofol and midazolam(Guo et al. 2016). Thus, in contrast to pro-inflammatory responses induced in macrophages in vitro, lymphocytic responses seem to shift to an anti-inflammatory (not-immunosuppressive) phenotype in-vivo(Sanders, Hussell, and Maze 2011).

Studies on humoral responses associated with dexmedetomidine infusion have demonstrated an intense anti-inflammatory effect in LPS-treated animals, with a significant reduction of TNFα and IL-6 circulating levels and with a significant improvement in mortality rate(Takumi Taniguchi et al. 2004, 2008). Similarly, a significant reduction in pro-inflammatory cytokines has been observed in clinical studies on critically ill patients comparing dexmedetomidine vs. midazolam(Memis et al. 2007) and dexmedetomidine vs. propofol(Venn et al. 2001). The difference between the pro-inflammatory effects exerted on cellular components of the innate immune system and systemic humoral effects (associated with reduced levels of pro-inflammatory cytokines) may be related to the α2-adrenoceptor agonist's different effect on CNS and adaptive immune system(Sanders, Hussell, and Maze 2011; Tracey 2007).

As a conclusion, α2-adrenoceptor agonists have complex interactions with the immune system and patients may benefit from α 2-adrenoceptor agonist sedation in many ways. In particular, dexmedetomidine presents humoral anti-inflammatory effects particularly during systemic inflammation, but it contemporaneously improves macrophage function and antiapoptotic activity for several immune cells(Ma et al. 2004; Sanders and Maze 2007).

3.7 Volatile anesthetics

Although several evidences exist on immunological influences of halogenates, most of them derive from studies using halogenates as general anesthetics, instead of sedative in the ICU. As example, a more reduced phagocytotic and microbicidal function has been described in-vivo for alveolar macrophages during anesthesia with isofluorane than with propofol(Kotani et al. 1998). Nevertheless, a wide variation on humoral inflammatory pattern has been described for a similar group of patients; in particular, animal studies suggest that inhalation of isoflurane at anesthetics concentrations induces gene expression of pro-inflammatory cytokines in alveolar macrophages within 2 hours(Kotani, Takahashi, et al. 1999). Similarly, increasing gene expression of pro-inflammatory mediators, such as IL-1b, IL-8, interferon-gamma and TNFα, have been observed in-vivo during isoflurane administration than propofol infusion(Kotani, Hashimoto, et al. 1999). On the other hand, other studies have demonstrated a suppressed cytokine production in mechanically ventilated animals with lipopolysaccharide-induced lung inflammation during inhalation with halothane with respect to thiopentone administration(Giraud et al. 2000). In particular, a reduced polymorphonuclear cells recruitment, TNFα, IL-6 concentrations in bronchoalveolar lavage fluids have been observed in this model. Interestingly, this halogenate-induced pro-inflammatory response in the lung was transient and reversed 20 hours after anesthetic withdrawn(Giraud et al. 2000). The different effects induced by halogenates on humoral inflammatory pattern might partially be related to the specific halogenate drug used and on the concentration applied to the patient. The immunomodulatory effects of volatile anesthetics might thus differ from anesthesia in the operating room to sedation in the ICU.

In 2000 Goto et al. have in-vivo demonstrated that sevoflurane does not influence the rate of neutrophil apoptosis, cytokine concentration or neutrophil counts at clinical dose(Goto et al. 2000). On the other hand, Isoflurane has been demonstrated to reduce the phagocytic capacity of all polymorphonuclear cells(Heine et al. 2000).

Similarly, Welch et al. have reported that halothane reversibly inhibits human neutrophil bacterial killing function probably affecting the neutrophils oxidative microbicide activity(Welch 1981). Indeed, ROS production by activated neutrophils is inhibited by halothane, enflurane, isoflurane, and sevoflurane(Kurosawa and Kato 2008). As Inhibition of ROS release by volatile

anesthetics results in the suppression of initial inflammatory responses, it might provide a therapeutically beneficial effect during condition caused by unbalanced inflammation, such as ventilator induced lung injury or ischemia-reperfusion injury(Kurosawa and Kato 2008).

Also, adaptive immune system is affected by halogenates. In particular, halotane, sevoflurane, isoflurane and enflurane have been demonstrated to suppress the release of IL-1 and TNFα from human lymphocytes(Mitsuhata, Shimizu, and Yokoyama 1995), reducing the immunocapacity of these cells against microorganisms and tumor cells. The exact mechanisms by which halogenates inhibit lymphocyte function are unclear; however, the caspase-mediated induction of lymphocyte apoptosis seems to have a role in this process. Indeed, isoflurane and sevoflurane have been demonstrated to induce apoptosis in human lymphocytes in a dose-dependent and time dependent manner(Kurosawa and Kato 2008; Matsuoka et al. 2001).

In conclusion, most reports conclude that halogenates may amplify inflammation more than propofol, particularly regarding cytokine genes expression. However, volatile anesthetics may hamper the bactericidal activity of alveolar macrophages more efficiently than propofol does. However, these inhibitory effects may contribute to anti-inflammatory responses, by regulating the secretion of pro-inflammatory cytokines implicated in the pathophysiology of systemic inflammation.

IV Conclusions

Psychological characteristics can have a profound impact on maladaptive biochemical and neuroendocrine responses to surgical stress, thus potentially affecting perioperative outcomes. Similarly, psychological therapies aimed at modulating patients' perioperative experiences might interact with physiological responses to stress and positively influence surgical outcomes. A multidisciplinary approach integrating physical (e.g. anesthesiologic and/or surgical procedures) and non-physical (e.g. Cognitive-Behavioral Therapies or narrative medicine approaches) therapies can be considered the best strategy to successfully improve surgical outcomes and should be routinely adopted in the perioperative period.

Although meta-analyses and randomized controlled trials aimed at demonstrating the influence of psychological interventions on surgical outcomes include studies adopting several different methodologies, small to large effects were obtained,

depending on type of intervention and measured outcome. A predominant anti-inflammatory and immunosuppressive pattern has been associated with sedatives use. Although these anti-inflammatory effects might be conceptually useful during uncontrolled systemic inflammatory response syndrome not associated with infections, the sedation-induced immunosuppression might increase susceptibility to microbial colonization and worsen outcome of septic patients. In the future, consideration of the immune effects of sedatives may play a role in their selection among critically ill patients, and their use may be tailored toward therapeutic manipulation of the immune response.

List of abbreviations

SIRS Systemic Inflammatory Response Syndrome

TNF Tumor Necrosis Factor

IL Interleukin

CBT Cognitive Behavioral Therapy

MBI Mindfulness Based Interventions

MBSR Mindfulness Based Stress Reduction

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This project has been funded with support from the European Commission. This publication [communication] reflects the views only of the author, and the Commission cannot be held responsible for any use which ma y be made of the information contained therein.