RESEARCH PROTOCOL:

1. Title

Effect of dexmedetomidine on delirium and postoperative cognitive dysfunction in patients undergoing orthopedic or vascular surgery under regional anesthesia.

2. Introduction

One of the most frequent post-operative complications in the elderly with an incidence of 5-50% are postoperative cognitive disorders, namely delirium and post-operative cognitive dysfunction which is diagnosed with psychometric testing. [1,2] Both delirium and Post-operative cognitive dysfunction have been associated with significant financial costs for the care of these patients both in- and out- of hospital, as well as reduced ability to carry out daily activities, which affects their quality of life and disrupts balance in their families. [1,3]

Many factors are thought to be involved in the pathophysiology of the phenomenon. It is believed that the physiological changes observed during the aging process render the brain prone to the occurrence of mental disorders in stress situations. For example, normal aging results in reduced brain cerebral blood flow, neuronal loss and decreased concentrations and activity of major brain neurotransmitters, all of which are believed to reduce normal brain reserves in cases of stress, metabolic disturbances or infection. [4] The major neurotransmitters involved in these processes are acetylcholine, dopamine, γ-aminobutyric acid and norepinephrine. Acetylcholine plays an important role in maintaining consciousness and it is thought to play a central role in the development of postoperative cognitive disorders. Aging reduces acetylcholine release and muscarinic receptor activity in the brain. [5] Almost all drugs used in anesthesia have anticholinergic properties as well as many commonly used drugs: furosemide, digoxin, theophylline, coumarin, prednisolone, cimetidine and ranitidine have anticholinergic properties [3,6]

Regarding the effects of the type of anaesthesia, regional or general, the results are contradictory:

- The type of anesthesia does not seem to affect the onset of postoperative delirium [7][20]
- Early postoperative cognitive dysfunction to be more common after general anesthesia, while three months postoperatively no difference is observed. [8]

These findings may, however, be due to the fact that most patients undergoing regional anesthesia receive intraoperatively sedation. Therefore, the occurrence of delirium and / or early postoperative cognitive dysfunction after regional anesthesia may be the result of the anticholinergic effects of drugs administered intraoperatively for sedation.

Dexmedetomidine is an imidazole derivative that acts as an agonist of α2-adrenergic receptors. α2-agonists are unique among agents that cause central nervous system suppression because they do not act through the GABA system, do not have anticholinergic effects, do not cause respiratory depression and display analgesic properties. [9]

The administration of dexmedetomidine for sedation in the Intensive Care Unit has been found to reduce the incidence of delirium [10] in both general population and patients undergoing cardiac surgery. [11] The effect of intraoperative administration of

dexmedetomidine on the onset of postoperative delirium or agitation has been studied in children only and there are no studies of the elderly undergoing surgery.

3. Purpose of the study

Primary outcome:

The present research protocol aims to elucidate the effect of intraoperative administration of dexmedetomidine as sedation agent on the appearance of postoperative delirium and postoperative cognitive dysfunction in elderly patients undergoing orthopedic or vascular surgical procedures under regional anesthesia.

Secondary outcomes:

The study will also assess:

1. The effects of dexmedetomidine on sleep quality during hospitalization of patients with the use of The Pittsburgh Sleep Quality Index (PSQI).
2. The effect of the anaesthetic technic on the development of postoperative chronic pain after total hip and knee replacement with the use of painDETECT screening questionnaire

4. Method

4.1. Design of the study

Prospective randomized clinical study

Parallel design in two groups

Randomized trial: equal ratio (1: 1) of the distribution of the participants in one of the two groups through simple randomization, creation of the random distribution with computer-generated random numbers (SPSS program)

• Monocentric: will be carried out at the Anesthesiology Department of the University Hospital of Heraklion

• Data analysis: primary principle of analysis "intention to treat ", supplemental analysis according to the "as treated" principle.

4.2. Suitability criteria:

4.2.1. Entry criteria

To include patients in the study, they should meet the following criteria:

- Age> 65 years old
- No contraindications for regional anaesthesia
- The patient knows writing and reading
- Remain in the hospital for at least four days
- Their expected postoperative survival is at least one year (on malignant neoplasms) and with a small chance of re-operation within three months.

4.2.2. Exclusion criteria

The study will exclude patients:

- who refuse to receive regional anesthesia or to participate in the study
- with central nervous system disease (infectious, metabolic, degenerative, neoplastic, or major psychosis)
- with severe vision or hearing impairment
- alcoholic or drug abusers
- in severe general condition or in end-stage neoplasia
- with regional anesthesia contraindications:
- with coagulation disorders
    - INR> 1.4
    - platelet count <100,000 / μl
    - active / uncontrolled bleeding
    - lack of coagulation factors
    - administration of anticoagulants / antiplatelet drugs in a prophylactic dose for thromboembolic episodes (prior to epidural puncture)
- inflammation at the lumbar region
- increased intracranial pressure of any cause or CNS tumor
- gaining less than 25 points in the Mini Mental Status Exam during the preoperative assessment.

4.3. Conduct of the trial

4.3.1. Basic perioperative care & monitoring:

Preoperative fasting and pre-treatment according to the routine of the department. Patients upon entering the operating theatre are attached to standard monitors (electrocardiogram 3 or 5-lead, oximetry, noninvasive measurement of blood pressure every 5 minutes) and venous access will be established. Anaesthesia and postoperative analgesia will be based solely on purely regional techniques with the following options:

A. Epidural anaesthesia / analgesia: Under local anesthesia epidural catheter will be placed at intravertebral spaces L2-L3 or L3-L4. Through the catheter there will be a titrated infusion with 0.76% ropivacaine to achieve anaesthetic block up to the T7-8 dermatomes. The catheter will remain for postoperative analgesia, using ropivacaine 0.2 % infusion.

B. Combined Spinal & Epidural anaesthesia / analgesia: Under local anesthesia epidural catheter will be placed at intravertebral spaces L2-L3 or L3-L4 while Spinal anaesthesia will be perfomed at L4 – L5 to achieve fast onset with the use of hyperbaric bupivacaine . The epidural catheter will be used intraoperatively when the operation is prolonged or spinal block insufficient and will remain for postoperative analgesia, using ropivacaine 0.2 % infusion.

C. Spinal anaesthesia in combination with femoral nerve blocking: Under local anesthesia, spinal anaesthesia will be performed at L3-L4 or L4-L5 spaces with the use of hyperbaric bupivacaine. At the end of surgery and after resolution of spinal anesthesia, femoral nerve block will be performed under ultrasound guidance for providing postoperative analgesia with 0.2 - 0.15% ropivacaine.

Patients intraoperatively will receive either dexmedetomidine (study group) or propofol for sedation according to the clinical practice (control group). The aim of intraoperative sedation will be to maintain the patient at stage 3 or 4 of the Ramsay sedation scale 3-4

During surgery, supplemental oxygen will be administered to the patient at a concentration such that saturation of hemoglobin in oxygen is maintained at or greater than 95%.

Where appropriate, infusion of phenylephrine or noradrenaline or small single doses of ephedrine will be administered to maintain hemodynamic stability.

Replacement of blood loss and fluid administration will be personalized according to patients' needs.

Postoperatively patients will receive oral paracetamol 1 gr every 8 hours, while in case of inadequate analgesia with regional techniques, tramadol 100mg will be administered.

4.3.2 Postoperative period

4.3.2.a Delirium assessment

All patients will be monitored daily for the immediate post-operative period for the appearance of confusion or delirium or for any anesthetic or surgical complications. For the diagnosis of delirium, the Confusion Assessment Method will be used to check:

A: the sudden appearance
B: fluctuation during the day
C: inability to concentrate
D: disorganized thinking

4.3.2.b Psychometric testing

The mental state of patients will be controlled by a group of psychometric tests, (European Psychometric Test - EUPT battery) that have been compiled by psychologists, have been successfully used, translated into many languages and modified appropriately to be credible internationally for surgical patients.

The tests to be used are:

1. Visual Verbal Learning Test [13]
2. Concept Shifting Task [14]
3. Stroop Colour-Word Test [15]
4. Letter-Digit Coding Test [16]

Postoperatively patients who will experience a reduction of> 20% of their performance in at least 2 of these trials will be considered to have Postoperative Mental Dysfunction.

In addition, the Cognitive Failure Questionnaire [17] and the Zung Self-Calibrated Depression Scale [18] will be used in the form of a questionnaire completed by the patient and a rough subjective indicator of his mental and psychological state.

Timeline of psychometric tests

Patients will undergo psychometric tests at three time points:

- Before anesthesia and during pre-anesthetic examination
- The fourth to seventh postoperative day and before the patient leaves the hospital, and
- Two - three months after surgery. If patients are unable to come to the hospital, they will be examined at home.

In all three sessions, patients will be examined by the same investigator, unaware of the type of sedation given to the patient.

5. Quality of sleep

The quality of sleep will be assessed with use of The Pittsburgh Sleep Quality Index (PSQI) which will be given to patients the day before surgery and all the postoperative days they will remain hospitalized

6. Chronic postoperative pain

The effect of the anaesthetic technic on the development of postoperative chronic pain after total hip and knee replacement will be assessed during the 2nd postoperative testing with the use of painDETECT screening questionnaire

Statistical Analysis

- Data management will be done with the help of a special software program with a computer.
- The analysis of the results will focus on the rate of delirium and post-operative cognitive dysfunction in relation to the type of sedation patients receive intraoperatively.
- Comparing the incidence of and post-operative cognitive dysfunction and delirium in patients in both groups will be tested by chi-square analysis and by step logistic regression.
- Sample size: A previous study in the population of Crete showed a frequency of 20% delirium in elderly surgical patients. [19] Considering the 10% reduction in delirium appearance, it was estimated that 120 patients per group with a 5% confidence level and a 30% confidence level [1-β] were required.

Reference

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