

## EPIDURAL ANESTHESIA FOR CAESAREAN SECTION IN A PATIENT WITH RISK OF MALIGNANT HYPERTHERMIA

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## EPIDURALNA ANESTEZIJA ZA CARSKI REZ KOD PACIJENTKINJE RIZIČNE NA MALIGNU HIPERtermiju

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### ABSTRACT

Malignant hyperthermia is a hypermetabolic disorder of skeletal muscle that occurs in genetically susceptible individuals after exposure to anesthetic. Basic disorder is an increase of calcium ions inside the skeletal muscle, increasing metabolism and reducing cell energy supplies leading to development of acidosis, cell membrane destruction and cell death. Due to the increased metabolism occurs hypercarbia and strong stimulation of the sympathetic nervous system (tachycardia, hypertension, ventricular arrhythmia, tachypnea dropped for the neuromuscular blockade). Sweating, cyanosis, muscle rigidity and hyperthermia are also present.

This work presents the case of a female patient aged 32 who was heterozygous for the mutation RYR1 gene and therefore has an increased risk of malignant hyperthermia. Per anamnesis we got data that patient's brother suffers from central core disease (myopathy). Patient has no muscle disease, 41<sup>st</sup> week of pregnancy and was admitted to the hospital for childbirth. Vaginal delivery in epidural analgesia was planned. Epidural catheter is placed in the space L3 - L4, through which she received 0.25% levobupivacaine 10 ml. Due to adverse obstetric findings cesarean section underwent after two hours. Given the increased risk of malignant hyperthermia, the safest type of anesthesia for cesarean is epidural anesthesia. Over the epidural catheter has received 0.5% levobupivacaine 18 ml. Anesthesia machine was verified, hoses were replaced with new ones, CO<sub>2</sub> absorber system was replaced, and whole system is flushed with pure oxygen, before surgery started. During the operation the patient had stable vital parameters that are monitored. She got a male child Apgar score of 9/10 and saw her child at birth. After the operation was transferred to the intensive care unit where we monitored the vital parameters, laboratory analysis, the amount and color of urine. Since all parameters were satisfactory, following day she was transferred to the ward, and she was discharged with a child on the fourth day after the surgery.

**Keywords:** Anesthesia, caesarean section, malignant hyperthermia

### SAŽETAK

Maligna hipertermija je hipermetabolički poremećaj skeletnih mišića koji nastaje u genetski osetljivih osoba, posle izlaganja anestetikim pokretačima. Osnovni poremećaj je povećanje kalcijumovih jona unutar skeletnih mišića, povećanje metabolizma i smanjenje energetske zaliha ćelija sa razvojem acidoze, destrukcije membrane ćelije i ćelijske smrti. Zbog povećanog metabolizma nastaje hiperkarbija i snažna stimulacija simpatičkog nervnog sistema (tahikardija, hipertenzija, ventrikularna aritmija, tahipneja izostaje kod neuromišićne blokade). Prisutno je znojenje, cijanoza, mišićni rigiditet, hipertermija.

U ovom radu prikazan je slučaj pacijentkinje stare 32 godine koja je heterozigotni nosilac mutacije RYR1 gena, te ima povišen rizik od maligne hipertermije. Rođeni brat boluje od centronuklearne miopatije. Ona nema mišićnu bolest, u 41. nedelji trudnoće je i primljena je u bolnicu radi porođaja. Planiran je vaginalni porođaj u epiduralnoj analgeziji. Plasiran je epiduralni kateter u prostoru L3 - L4, preko koga je dobila 0.25% levobupivakain 10 ml. Posle dva sata, zbog nepovoljnog akušerskog nalaza urađen je carski rez. S obzirom na povišen rizik od maligne hipertermije, najbezbednija vrsta anestezije za carski rez je epiduralna anestezija. Preko epiduralnog katetera je dobila 0.5 % levobupivakaina 18 ml. Pre operacije je proveren aparat za anesteziju. Stavljena su nova creva, zamenjen CO<sub>2</sub> apsorber, sistem ispran čistim kiseonikom. U toku operacije pacijentkinja je stabilnih vitalnih parametara koji se prate na monitoru. Dobila je muško dete Apgar score 9/10. Videla je svoje dete na rođenju. Nakon operacije je prevedena u jedinicu intenzivnog lečenja gde su praćeni vitalni parametri, laboratorijske analize, količina i boja urina. Kako su svi parametri bili zadovoljavajući sutradan je prebačena na odeljenje i četvrtog dana od operacije otpuštena kući sa detetom.

**Ključne reči:** Anestezija, carski rez, maligna hipertermija



## ABBREVIATIONS

MH - Malignant hyperthermia



## INTRODUCTION

Malignant hyperthermia (MH) is a hypermetabolic disorder of skeletal muscle that occurs in genetically susceptible individuals after exposure to anesthetic. Basic disorder is an increase of calcium ions inside the skeletal muscle, increasing metabolism and reducing cell energy supplies leading to development of acidosis, cell membrane destruction and cell death (1). Due to the increased metabolism occurs hypercarbia and strong stimulation of the sympathetic nervous system (tachycardia, hypertension, ventricular arrhythmia, tachypnea dropped for the neuromuscular blockade). Sweating, cyanosis, muscle rigidity, hyperthermia and rhabdomyolysis are also present (2, 3, 4).

Triggers of MH in patients with a genetic predisposition are all inhalation anesthetics (excluding  $N_2O$ ), and depolarizing muscle relaxant succinylcholine (1, 2).

MH crisis can occur at any time during the perioperative period.

The earliest described examples of MH are deaths of two members of the same family, mother and son (on 1915 and 1919) who received anesthetic chloroform and diethyl ether. Muscle rigidity is described during the operation (5). MH was described in more details and it was explained that it is a hereditary disease by Deuborgh 1962 (6).

The incidence of MH differs between countries from 1:10.000 – 1:250.000 anesthesia (2). Incidence in children is 1:15.000, and it is more often in men. In Denmark, the incidence of fulminant MH is 1:250.000 in general anesthesia, but it is significantly increased when combined inhalation anesthesia with succinylcholine, to 1:62.000 (7). It is estimated that in France 1:2.000- 1:3.000 people carry a mutation susceptibility to MH. The prevalence in the Japanese population can be more than 1:2.000 of people (8).

Mortality rate of MH ranges from 5-30% (1).

## CASE REPORT

The patient who is 32, in 41<sup>st</sup> weeks of pregnancy was admitted to the hospital for delivery. Since a large percentage of deliveries performed in epidural analgesia in our hospital, patient was interested in such a manner childbirth. Prior to labor epidural analgesia it was required for patient to be examined and informed about epidural analgesia by the anesthesiologist. The patient had anesthetic examination at the beginning of the ninth month of pregnancy.

The personal history of the patient states that chronic diseases glomerulonephritis is present. She has regularly nephrology examinations and she has not receiving thera-

py. At the age of five she had an appendectomy, anesthesia was without complications. She claims that she had examination for “lesser controlling ability of the fourth and fifth fingers of her left hand”, four years ago. Electromyoneurography finding was described as clear. She is allergic to penicillin.

In the family history says that her brother was suffering from central core disease (myopathy). When her brother did genetic testing, he found that he is the holder of two variants of the gene RYR1, both paternal and maternal one. The patient's mother had a caesarean section, without anesthesiology complications. At the time of examination the patient was in the process of genetic tests, expecting results.

In laboratory analyzes of blood count was in normal values, sterile urine culture, the examination of urine protein +/-, sediment Le 2-3, 3-4 shriveled Er., Proteinuria Esbach at 0,160g /24h.

Due to family history of the patient, she was asked to perform examination by a neurologist and to bring the results of genetic tests before admission to the hospital. Patient brought required reports. Genetic testing determined that patients is heterozygous for the mutation RYR1 gene, causing elevated risk of malignant hyperthermia. Neurological examination did not gave clinical signs of neurological diseases, except that hypoesthesia of fourth and fifth fingers of her left hand is still present.

After 41 weeks pregnant patient was admitted to our hospital with painful contractions. The obstetrician report states dilation of the cervix 3-4 cm., cardiotocography (CTG) was made and oxytocin stimulation was included. Given that the patient wanted to give birth in epidural analgesia, reexamine by the anesthesiologist and access to medical files were necessary. It was required for her to sign off before delivery that she is informed on epidural anaesthesia, confirming that she wants vaginal delivery in epidural analgesia and that she is familiar with the procedure and possible complications. The patient was connected to the monitor, peripheral intravenous cannula was sited, and 500ml crystalloid included. Patient's status: TA 120/80 mmHg, ECG - sinus rhythm f 82/min, SatO<sub>2</sub> 99%, afebrile, auscultatory findings of the heart and lungs normal, Visual Analogue Scale (VAS) score of 6, body weight 65kg, height 157cm, BMI 25.6, ASA II. Upon expiry 500ml crystalloid continued with crystalloid infusion and the patient was placed in a sitting position, with spinal flexion. Anesthesiologist identified the space L3 - L4. In aseptic conditions, surgical cleaning and garnish of lumbar spine was performed. In the space L3 - L4 local anesthesia was given



to patient, 2 ml of 2% lidocaine, and then the epidural space was identified using loss of resistance technique. For the test we gave 3ml dose of 1% lidocaine and epidural catheter was placed. We gave 10ml 0.25% levobupivacaine on the epidural catheter after five minutes. The pain was reduced, VAS score of 1 after 15 minutes, without motor blockade, with sensory blockade Th11-Th12. Monitored vital parameters were all the time without deviations. TA about 110/65 mmHg, pulse f 75/min, CTG monitored. Obstetric examination, two hours later, established adverse obstetric finding, dilation phase stasis, and decision to perform caesarean section was made. TA 130/80 mmHg at that moment, and f around

110 probably due to patients upset. Through the epidural catheter we gave 18ml 0.5% levobupivacaine, iv ranitidine 50mg, urinary catheter was placed and patient was transferred into the operating room. In the operating room the vital parameters were monitored on a monitor, patient receives O<sub>2</sub>, crystalloid infusion, and motor block appears. TA ranges from 100/60 mmHg to 115/70 mmHg, pulse 75-85 f/min, SatO<sub>2</sub> 100%, urine clear. The baby was born five minutes from the start of the operation, male, Apgar score of 9/10. The mother saw her newborn baby at birth, and in the further course of the operation wanted to sleep, and received iv. 2mg of midazolam. Upon completion of the operation, which lasted 30 minutes epidural catheter was removed, the patient was feeling well and was extremely satisfied with the anesthesia. Cesarean section was performed in the afternoon, and the patient first was verticalized the next morning. Laboratory analyzes were repeated - blood count, glucose, electrolytes, urea, creatinine, and CK were at the reference values. On the fourth day after the caesarean section the patient was discharged from the hospital with her child.

## DISCUSSION

MH is a hypermetabolic disorder of skeletal muscle, it includes central core disease, multi-minicore myopathy, King Denborough syndrome (9).

MH is a heterogeneous disorder where in 80% of cases, a mutation of the gene for the ryanodine receptor (*RYR1*) with the location on chromosome 19q13.1. The main problem in the skeletal muscle of an increase myoplasmic Ca<sup>2+</sup> concentration, which is responsible for the calcium channel in terminal tanks sarcoplasmic reticulum, known as the ryanodine receptor. It is a dominant type of inheritance with variable penetrance (1).

Clinical status and its severity of the syndrom may be different. Although muscle rigidity and extreme temperature jump are most dramatic signs of the crisis, the crisis itself starts with unexplained and progressive tachycardia, followed by ventricular tachyarrhythmia. Tachycardia almost always occurs prior to raising the temperature and muscle rigidity. Cardiac arrhythmias are caused by the heart muscle rigidity, acidosis, electrolyte imbalance and

increased body temperature. Blood pressure becomes unstable. In patients on spontaneous breathing occurs tachypnea. Increase in the concentration of the expiratory carbon dioxide occurs, which is the result of hypermetabolism musculature. Canister with absorbent for carbon dioxide is hot, and the blood from surgical wound becomes dark, and cyanosis is present. Muscle rigidity usually develops on the extremities, chest and masseter, but sometimes it may be absent (non-rigid form of malignant hyperthermia). One of the alternative forms MH is masseter muscle spasm that occurs soon after giving succinyl-choline in endotracheal intubation (6). Body temperature increases every five minutes to 1-2 degrees (Celsius). The most specific and the most sensitive sign is the increase in carbon dioxide at the end of expiration (ETCO<sub>2</sub>). Clinical picture is accompanied by pH value decline due to the associated metabolic and respiratory acidosis (1, 6).

Body temperature may exceed 43 degrees (Celsius), PaCO<sub>2</sub> > 100mmHg, pH <7.0 (10).

Start of MH crisis was accompanied by a high increase serum calcium and potassium, and then their significant decline after 1-2 hours. Serum phosphorus, magnesium, sodium, glucose, lactate and pyruvate are growing. Large molecules leave the muscle cell few hours after the onset of the crisis: creatinine phosphokinase (CPK), lactic dehydrogenase (LDH), glutamine-oxaloacetic transaminase (SGOT), aldolase and myoglobin. Myoglobin causes vasoconstriction and acute renal insufficiency. Myoglobinuria appears. Later complications include acute renal insufficiency, disseminated intravascular coagulopathy, cerebral edema, seizures, liver insufficiency and recurrence of MH crisis with an incidence of 25% within 24-36 hours (1).

The 'gold standard' for the diagnosis of malignant hyperthermia is in vitro contracture test which is based on contracture of muscle fibers in the presence of halothane and caffeine (2).

Discovering various RYR1 caused mutation of MH, molecular genetic test are introduced to clinical practice (1).

The first and most important in the process of MH crisis is immediate interruption of all anesthetics and muscle relaxants which are known to be triggers reactions, followed by hyperventilation of lungs with pure oxygen, at a flow rate of 10 l/min. Surgery supposed to be finished as soon as possible. In addition to standard monitoring, which includes ECG, pulse oximetry, and capnography, central venous catheter and arterial line need to be placed, body temperature and diuresis to be monitored. If used inhalation anesthetic, replacement the corrugated hose, balloon, and canister absorber is required. In the treatment of MH, following guidelines, we should use dantrolene which inhibits the release of calcium from the sarcoplasmic reticulum. This is a muscle relaxant, a derivative of hydantoin. Given doses are 2.5 mg/kg, to be repeated if necessary to 10mg/kg. Continuation of dantrolene therapy is 1 mg/kg every 6 hours over the





next 24-36 hours. In addition to dantrolene therapy involves rehydration, correction of metabolic and respiratory acidosis, control heart rhythm (Ca blockers should not be given because of the interaction with dantrolene), cooling, treatment of hyperkalemia, maintenance of diuresis and coagulation factors. Laboratory analyzes need to be repeated and corrected (1, 2).

It is recorded that the muscular abnormalities are present in 67% of patients with genetic defects in MH and 36% of the first line of inheritance. Kyphosis, kyphoscoliosis, lumbar lordosis, multiple hernias, ptosis and strabismus can be included. (6). Our patient did not have any of these diseases, but she cannot clench her left fist, and she has glomerulonephritis. Since her brother has central core disease, and her genetic testing determined to be heterozygous for the mutation RYR1 gene, she was treated as a patient susceptible to MH. Pregnant women who know they are at risk for MH are advised to consult the anesthesiologist before labor (11). Thus, our patient was examined by anesthesiologist at the beginning of the ninth month of pregnancy. It is recommended that an anesthetic team is notified when such a patient is admitted to the hospital, in order to prepare. With our patient, the vaginal delivery in epidural analgesia was planned. When she was admitted to the maternity ward anesthesia machine was prepared in case of emergency caesarean section, which later happened. It is recommended that the apparatus for anesthesia replace all hoses and CO<sub>2</sub> absorber, anesthetic machine to be flushed with high flow rate oxygen 10 l/min, duration 1 hour (1, 12). The use of the active carbon filter is recommended in apparatus preparation for anesthesia (13).

Epidural analgesia reduces stress associated with labor and reduce the demand for oxygen during childbirth (14). Therefore we placed epidural catheter and gave 0.25% levobupivacaine 10ml, leading to patient's pain relief and reducing fear of childbirth. On the monitor, we tracked blood pressure, heart rate and frequency, periodically measured body temperature. To women with MH susceptibility, it is recommended regional anesthesia for caesarean section, in cases it is not an emergency caesarean section. Local anesthetics of the amide group are considered safe. Dantrolene is not given in the prophylaxis (12). Our patient received 18ml of 0.5% levobupivacaine for cesarean section and there were no complications during and after surgery.

In medical journals it has been discussed case of anesthesia for elective Caesarean section at 21 year old patient with central core disease. Central core disease is characterised by muscle weakness, skeletal deformities and susceptibility to malignant hyperthermia. Total intravenous anaesthesia was used because of the combination of potential malignant hyperthermia, severe kyphoscoliosis and extensive spinal scarring. Administered anesthetic agents were propofol, remifentanyl and rocuronium as muscle relaxant. Surgery went without complications. Recovery and extubation proceeded smoothly, and the patient was

discharged to the ward under midwife care. The baby was initially apnoeic and required two doses naloxone at 3 and 5 min. His apgar scores were 3, 7, and 9 at 1, 5, 10 min respectively (15).

Another interesting case has been described in Japan at 26 year old patient with elective Caesarean section, with past history of fulminant malignant hyperthermia. Hyperthermia and subsequent cardiac arrest occurred during general anesthesia when she had been planned to perform hip joint arthroplasty at the age of 7. The Caesarean section was performed under spinal anesthesia with hyperbaric tetracaine. Prophylactic oral dantrolene administration started 4 days before the operation and on the day of the operation. Intravenous dantrolene was administered during the operation and the day after surgery. No clinical symptoms of MH occurred during perioperative period (16).

In the United States, the Malignant Hyperthermia Association of the United States (MHAUS) provides Newsletters, printed information, website (17) to meet the needs of the various groups interested in MH. The European MH group (18) coordinates testing procedures throughout Europe and is made up of professionals investigating MH. Patient supported MH associations exist in France, Germany, Switzerland, Japan, United Kingdom and several other countries.

These organizations have been crucial to the education of anesthesia providers in diagnosing and managing MH and helping patients better understand the disorder.

Concerning the above our patient was informed about the risk for MH and possible complications.

## CONCLUSION

MH is a serious condition with a high mortality rate. MH susceptibility patients, who need to undergo surgery should be considering regional anesthesia, as much as possible. In case that general anesthesia is necessary, safe medicines need to be chosen, and anesthesia machine needs to be particularly prepared for such patients. Dantrolene is not given prophylactically.

Wider introduction of the practice of genetic tests reduces unexpected and unwanted events in anesthesia.

All interested and informed clinicians and families are the best patients allies against the MH complications.

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