

MEDICATION AND REGULATION OF ACUTE POSTOPERATORY PAIN, USING MULTIMODAL THERAPY

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MEDICATION AND REGULATION OF ACUTE POSTOPERATORY PAIN, USING MULTIMODAL THERAPY (Abstract): Surgical interventions and opioid exposure activate both peripheral (satellite glial cells) and central glia (microglia and astrocytes), contributing to peripheral and central sensitization and maintenance of pain. Specific molecules such as MMP-9 and IL-1 β are involved. **Materials and methods:** We analyzed female patients who presented for emergency or elective abdominal surgery at the “Cuza-Voda” Hospital of Obstetrics and Gynecology Iași, Romania and who met the following inclusion criteria and did not present any of the exclusion criteria were included in the analysis. Inclusion criteria: Age over 18 years; Surgical obstetrical or gynecological indication. exclusion criteria: patients under 18 years of age; people with suspected sepsis or serious medical comorbidities such as heart failure, undiagnosed fever and instable state. The study was retrospective and prospective, during January 2024 to November 2025, starting from the clinical parameters, surgery indication, analyzing clinically and paraclinically, the importance of intra- and post-operative analgesic medication that was used. **Results:** Of the total study group, 52.3% of patients underwent cesarean sections (CST), 14.4% underwent total hysterectomy with bilateral adnexectomy (HT+AB) and 9% underwent biopsy curettage, the rest of gynecological surgeries consisted of Madden mastectomy, salpingectomy, ovarian cyst removal. Multimodal drug therapy and opioid treatments were required to achieve the control of post operative pain. **Conclusions:** Current areas of interest in pain research include investigating the effect of mood on pain processing in the brain and the search for new drugs to block the channels involved in pain transmission, and the actual important post operative pain therapy involves a combination of multimodal and opioid treatments. **Keywords:** PAIN, RECEPTOR, POLYMORPHISM, OPIOID THERAPY, MULTIMODAL TREATMENT.

INTRODUCTION

Pain is one of the most subject symptoms concerning patient care in healthcare. Primary afferent fibers, A δ and C fibers that carry noxious sensory information, are extra primary A β fibers that carry non-noxious stimuli (1). Each of these fiber types has different characteristics that allow the transmission of certain types of sensory information (2). A β fibers are

heavily myelinated and of large diameter, thus allowing rapid signal conduction. They have a low activation threshold and usually respond to light touch and transmit innocuous stimuli. A δ fibers are lightly myelinated and of smaller diameter and, therefore, conduct more slowly than A β fibers. They respond to mechanical and thermal stimuli. They interpret fast, sharp pain and are responsible for the initial re-

flex response to acute pain (3). C fibers are unmyelinated and are also the smallest type of primary afferent fiber. Therefore, they demonstrate slow conduction. C fibers are polymodal, responding to chemical, mechanical, and thermal stimuli. C fiber activation results in slow, burning pain. These reactions have been studied in orofacial surgery, neurological diseases, and general surgery (4, 5).

Peripheral sensitization is a state of hypersensitivity and hyperexcitability of nociceptors, caused by inflammation and injury. It involves activation of a variety of ion channels and protein kinases (6). Central sensitization: Persistent nociceptive stimulation leads to changes in the central nervous system, involving increased excitability of neurons in the spinal cord and brain. This contributes to chronic pain (7, 8, 9). Glial activation and neuroinflammation after surgery/opioid treatment: Surgical interventions and opioid exposure activate both peripheral (satellite glial cells) and central glia (microglia and astrocytes), contributing to peripheral and central sensitization and maintenance of pain. Specific molecules such as MMP-9 and IL-1 β are involved and more research is required to understand this process (10, 11, 12).

MATERIALS AND METHODS

Study perspective. We analyzed 111 female patients who presented for emergency or elective abdominal surgery at the “Cuza-Voda” Hospital of Obstetrics and Gynecology Iași, Romania and who met the following inclusion criteria and did not present any of the exclusion criteria.

The study was retrospective and prospective, during December 2024 to December 2025, starting from the clinical parameters, surgery indication, analyzing clinical-

ly and paraclinically, the importance of intra- and post-operative analgesic medication that was used.

Inclusion criteria were formed by: age above 18 years; associated obstetrical or gynecological surgical intervention.

Exclusion criteria were patients under 18 years of age; persons with suspected sepsis or associated severe medical pathologies

The general objective was evaluating the effectiveness of the treatment of moderate to severe postoperative pain in patients who present major risk factors for having an unusually high level of acute postoperative pain.

Statistical analysis. Descriptive and analytical methods were used in the statistical analysis. After collecting the data, in an accessible form to ensure their informational character, their processing was carried out. The data were centralized in *Excel* and *SPSS* databases and processed with the statistical functions to which they lend themselves. In the presentation of the data, confidence intervals at the 95% significance threshold were used, and the χ^2 and t-Student tests were used to test the differences. The normality testing of quantitative value series was performed with the Kolmogorov-Smirnov test used to test large data sets. The threshold chosen in testing the null hypothesis is $p > 0.05$, therefore the variables are normally distributed. Normality tests Skewness or Kurtosis, which often involve skewness, assess whether the distribution of a data set resembles a normal distribution. Skewness measures the skewness of the Linear regression, by the method of least squares, was the modeling method used. It is the method called “regression”, “linear regression”, “multiple regression” or “least squares” when building a model.

RESULTS

Particularities of the drug treatment used before hospitalization

Before the surgical intervention, 8.6% of the patients with cesarean section (CSS) received Aspenter 75 mg, 100 mg, respectively 150 mg and 15.5% other medication such as Euthyrox for thyroid pathology, Metformin for diabetes pathology, while patients with interventions such as total hysterectomy with bilateral adnexectomy (HT+AB) did not receive medication before the surgical intervention ($p = 0.002$).

Type of surgery performed and surgical outcomes

Of the total study group, 52.3% of patients underwent cesarean sections (CST), 14.4% underwent total hysterectomy with bilateral adnexectomy (HT+AB) and 9% underwent biopsy curettage, the rest of gynecological surgeries consisted of Madden mastectomy, salpingectomy, ovarian cyst removal.

Cesarean section results (CST). Of the 58 patients with cesarean section, 79.3% were under 36 years of age, while 83% of patients with other types of surgery were over 36 years of age ($p = 0.001$).

In patients with cesarean section, the series of values for gestation, number of weeks of pregnancy, birth weight, Apgar and number of days of hospitalization are distributed with the values of the Kurtosis test > 2 and the values of the Kolmogorov-Smirnov test < 0.05 , while the series of values for parity varies in the range 1-4; group mean 1.72 ± 0.76 ; median 2; Kurtosis test result 1.249 and $p > 0.05$ in Kolmogorov-Smirnov test, which suggests that statistical significance tests can be applied for continuous variables.

Before surgery, 8.6% of patients with cesarean section received aspirin and 15.5% other medication, while patients with HT+AB did not receive medication before surgery ($p = 0.002$).

Demographic features of analyzed patients according to the medication

Of the 17 patients treated intraoperatively with Mialgin, 88.2% were over 36 years old ($p=0.001$) and 64.7% came from urban areas ($p=0.424$). Of the 30 patients treated intraoperatively with Fentanyl, 73.3% were over 36 years old ($p = 0.003$) and 76.7% came from urban areas ($p = 0.219$). Of the 12 patients treated intraoperatively with Diazepam, all were under 36 years old ($p = 0.001$) and 66.7% came from urban areas ($p = 0.532$). The only patient treated intraoperatively with Phenobarbital was under 36 years old and came from rural areas, and the patient treated with Morphine was over 36 years old and came from rural areas.

Associated pathologies and the association with the medication

Of the 17 patients treated intraoperatively with Mialgin, 35.3% had iron deficiency anemia ($p = 0.494$), 29.4% adhesion syndrome ($p = 0.053$) and 17.6% uterine fibroids ($p = 0.071$). Of the 30 patients treated intraoperatively with Fentanyl, 36.7% had iron deficiency anemia ($p = 0.359$), 26.7% postoperative adhesion syndrome ($p = 0.019$), 10% hereditary thrombophilia ($p = 0.283$), 6.7% had hypertension ($p = 0.177$) and 3.3% diabetes mellitus ($p = 0.705$). Of the 12 patients treated intraoperatively with Diazepam, 25% had uterine fibroids ($p = 0.027$), 16.7% iron deficiency anemia ($p=0.184$), 16.7% adhesion syndrome ($p = 0.506$) and 8.3% had hereditary thrombophilia ($p = 0.562$).

Hospitalization period, according to OG surgical interventions performed

Treatment with analgesics, depending on the surgical intervention, highlights the following aspects (fig. 1):

- 8.6% patients with cesarean section (CST), were treated intraoperatively with Fentanyl (p = 0.001);
- 62.5% of patients with total hysterectomy with bilateral adnexectomy (HT+AB) were treated intraoperatively with Fentanyl (p=0.001);
- 40% patients with classical or laparoscopic unilateral ovarian cystectomy were treated intraoperatively with Fentanyl and

20% with Diazepam (p=0.001);

- 33.3% of patients with interventional hysteroscopy were treated intraoperatively with Mialgin and 33.3% with Fentanyl (p = 0.001);
- among patients with classical or laparoscopic uterine myomectomy, 50% were treated intraoperatively with Mialgin, 50% with Fentanyl and 50% with Diazepam (p = 0.001);
- among patients with Madden-type radical mastectomy, 50% were treated intraoperatively with Mialgin, all patients with Fentanyl and 50% with Diazepam (p = 0.001).

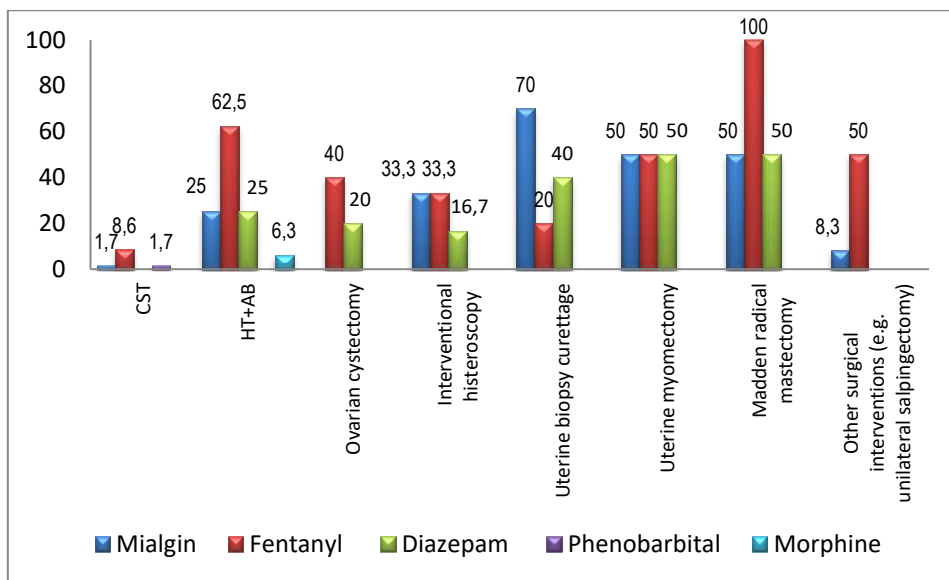


Fig. 1. Correlation of medication with type of surgical intervention

Intraoperative drug treatment

Ibuprofen, dosage 400 mg injectable solution / 100 mL was administered intraoperatively in 1 to 3 doses to 25.9% of patients with CST and 17% of those with other types (p=0.258) .80% of the patients with CST, 33.3% of those with ovarian cystectomy and all with HT+AB received a

single dose of Ibuprofen (p=0.329). Paracetamol, 10 mg/mL 100 mL was administered intraoperatively in 1-4 doses to 89.7% of the patients with CST and 79.3% of those with other types (p = 0.130). A total of 51.9% of the patients with CST, 66.7% of those with hysteroscopy or biopsy uterine curettage received a single dose of Parace-

tamol, while 38.5% of the patients with CST, 50% of those with myomectomy or mastectomy received two doses of Paracetamol. Three doses were received by 53.3% of patients with HT+AB, 50% of those with myomectomy or mastectomy and all with ovarian cystectomy ($p=0.001$).

Mabron, dosage 50 mg/mL 2 mL was administered intraoperatively in 1-3 doses to 93.1% of patients with CST and 49.1% of those with other types ($p = 0.001$). 70.9% of patients with CST and all with mastectomy received a single dose of Mabron. Two doses were received by all with ovarian cystectomy, 61.5% of patients with HT+AB, 50% of those with myomectomy, 27.5% of patients with CST ($p = 0.004$).

Algocamin, dosage 1 g/2 mL was administered intraoperatively in 1-4 doses to 89.7% of patients with CST and 64.2% of those with other types ($p = 0.001$). For 51.9% of patients with CST, 50% with ovarian cystectomy or myomectomy, 33.3% with hysteroscopy or biopsy curettage they received a single dose of Algocamin. All patients with mastectomy, 66.7% of patients with biopsy curettage, 50% of those with HT+AB, 44.2% of patients with CST received two doses ($p = 0.041$). Only 14.3% of patients with HT+AB received four doses.

Acupan, dosage 20 mg/2 mL was administered intraoperatively in 1-3 doses to 65.5% of patients with CST and 37.7% of those with other types ($p=0.004$). 86.8% of patients with CST, all with hysteroscopy, biopsy curettage, myomectomy, or mastectomy received a single dose of Acupan. All patients with ovarian cystectomy received two doses, 50% of patients with HT+AB, 13.2% of patients with CST ($p = 0.049$). Only 12.5% of patients with HT+AB received three doses.

Refen, dosage 25 mg/3 mL was administered intraoperatively in 1-4 doses to 82.8% of patients with CST and 73.6% of those with other types ($p = 0.243$). 83.8% of patients with uterine biopsy curettage, 72.9% of patients with CST, 66.7% with hysteroscopy and 15.4% with HT+AB received a single dose of Refen. All patients with ovarian cystectomy or mastectomy, 50% of patients with myomectomy, 30.8% of those with HT+AB and 25% of patients with CST received two doses ($p = 0.005$). Four doses were received by only 7.7% of the patients with HT+AB.

Postoperative drug treatment

Postoperative treatment with Clexane was received by 76.6% of the patients in the present study group, all patients with myomectomy, 93.1% of the patients with CST, 81.3% of the patients with HT+AB, 60% with ovarian cystectomy, 50% with mastectomy, 33.3% with hysteroscopy and 30% with biopsy curettage ($p = 0.001$).

Postoperative treatment with Cefotax was received by 17.1% of the patients in the present study group, including all patients with myomectomy, 50% of the patients with HT+AB, 40% with ovarian cystectomy and 33.3% with hysteroscopy ($p = 0.001$). Refen, 25 mg/3 mL was administered postoperatively in 1-22 doses to 82.8% of patients with CST and 60.4% of those with other types ($p = 0.004$). 50% of patients with myomectomy, 33.3% of patients with biopsy curettage, Algocamin, dosage 1 g/2 mL was administered postoperatively in 1-16 doses to 74.1% of patients with CST and 52.8% of those with other types ($p=0.020$). 50% of patients with mastectomy, 33.3% of patients with HT+AB and 20.5% of those with CST received postoperatively 1-2 doses of Algocamin. All patients with myomectomy, 58.2% of patients with CST, 33.3% of patients with

ovarian cystectomy and 8.3% of those with HT+AB received 3-5 doses of Algomamin postoperatively. More than 5 doses of Algomamin were received by all patients with hysteroscopy, 66.7% of patients with ovarian cystectomy, 58.4% with HT+AB, 50% of those with mastectomy and 20.5% of patients with CST ($p = 0.005$). The morphine receptor mutation (OPRM1) was more frequently present in patients with biopsy curettage (60%), myomectomy (50%), mastectomy (50%), hysteroscopy (33.3%), CST (20.7%) and ovarian cystectomy (20%) ($p = 0.048$). There were no statistically significant differences by age group ($p = 0.785$).

DISCUSSION

Cesarean rates in Romania are increasing at a total of 60% of births. Our results show that caesarean sections were performed in 79.3% of cases in patients younger than 36 years of age. Pain management with opioids and anxiolytics during and after this type of surgery was managed with Mialgin in 17 patients, Diazepam in 12 patients, Fentanyl in 8.6% of cases.

Opioids bind to and stimulate opioid receptors (μ , κ , and δ) that are found in the brain, spinal cord, peripheral nervous system, and gastrointestinal tract. Opioid receptors are a type of G protein-coupled receptor and are found in the central and peripheral nervous systems and are involved in many aspects of nervous system function, including sympathetic and parasympathetic activity and pain modulation. (18, 19). Because exogenous opioids, such as morphine and fentanyl, perform the same action as enkephalins at the receptor level, they can have an effect anywhere, especially in the midbrain, pons, medulla, and spinal cord (7).

In terms of pain modulation, studies describe that some signals from the sensory cortex or from afferent fibers travel along the spinothalamic tract ending in the periaqueductal gray area of the midbrain. Endogenous opioids are released, enkephalins, which stimulate neurons with fibers that transmit information to the locus coeruleus within the brainstem pons and the locus raphe magnus in the medulla. (10, 21). Our study followed the usage of dexamethasone as a co-administration during the induction phase of the regional analgesia, before blockage pain installment, because it can reduce pain by blocking the intracellular conversion of phospholipids to arachidonic acid, and our study found it beneficial for pain management (16, 17).

In our study intraoperative drug treatments consisted of 1-3 doses of Ibuprofen in 25.9% of caesarean surgeries, 33.3% of ovarian cystectomies and at least one dose in all cases of hysterectomies. More than half of patients received a dose of Paracetamol, while larger surgeries such as mastectomies and myomectomies received 2 doses. Analgesics, such as, non-steroid anti-inflammatory pills (NSAIDs), as ibuprofen, block the synthesis of all prostaglandins, including PGI₂ (prostacyclin), thereby slowing or stopping inflammation (13). The inflammatory process and pain reduction occur by blocking the formation of PGE₂. This is achieved by blocking COX-1 and COX-2. COX-1 is found in low concentrations in a balanced proportion throughout the body, and COX-2 is the inducible form, which is dramatically increased during inflammatory states, such as immediate post operative phase (14, 15).

Mabron, tramadol, an opioid analgesic, that relieves pain by acting on specific nerve cells in the spinal cord and brain was administered in 93% of caesarean surgeries

and in 49.1% of total surgeries described.

Algoalmin an analgesic and antipyretic with indications that include severe post-injury or postoperative pain, was prescribed in up to 4 doses in 89.7% of caesarean surgeries and more than half of all other surgeries.

Acupan, an analgesic symptomatic treatment of short-term painful conditions, in particular post-operative pain was administered in 65.5% of caesarean sections and 37.7% of all other surgeries, during the intraoperative period and did not require multiple doses except for 15% of total hysterectomies.

Refen is a non-steroidal anti inflammatory drug that has the active substance diclofenac sodium. Refen is presented as an injection/infusion solution and is used to treat acute pain.

Our study described its utility in more than 72% of caesarean sections, half of uterine gynecological surgeries, with up to 4 doses in 7.7% of cases during the intraoperative period.

Multimodal pain management offers a comprehensive strategy to improve function and quality of life while minimizing opioid use. Increasing access to interventional pain techniques through collaboration between surgeon and anesthesiologist can make an important difference between poorly controlled pain and a stable, comfortable postoperative patient.

Minimizing pain enhances long and short - term quality of life, reduces complications in the immediate and late postoperative phase and increases confidence in the surgical act and in the postoperative recovery time.

CONCLUSIONS

Multimodal analgesia is used to characterize the use of combinations of drugs with

different modes of action. In this way, it is possible to use lower doses of drugs, thus minimizing unwanted side effects.

By using a combination of NSAIDs and opioids for postoperative pain, the amount of opioid required is much lower and opioid-related side effects become less significant. Pain is both a sensory and emotional experience, and patients' previous experiences, fears and anxieties can play an important role. Pain transmission is the result of complex peripheral and central processes. These processes can be modulated at different levels, and pain perception is the result of the balance between facilitatory and inhibitory interactions.

Current areas of interest in pain research include investigating the effect of mood on pain processing in the brain and the search for new drugs to block the channels involved in pain transmission.

Thus, in the pathophysiology of pain it is important to understand that: the pain experienced by patients is the result of the interaction between sensory and emotional experiences. A δ fibers transmit fast, sharp, localized pain. C fibers transmit slow, diffuse, dull pain.

Pain transmission can be modulated at several levels, including the dorsal horn of the spinal cord and by descending inhibitory pathways. The spinothalamic and spino-reticular tracts are important ascending pain transmission pathways. Neuropathic pain can be spontaneous and is often described as a burning sensation or can be felt very strongly by the patient.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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