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The rationale for the choice of preventive intraoperative anesthesia for uterine curettage in patients with individual intolerance to amide anesthetics

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Abstract. Background. Uterine curettage (UC) is widely used in global clinical practice owing to its great diagnostic and therapeutic value. At the same time, UC leads to a damage to the integrity of soft tissues, causing development of postoperative pain syndrome. Some patients have an individual intolerance to amide anesthetics, which limits their use in this cohort. Purpose: to improve the quality of providing anesthetic care in the early postoperative period after UC to women who have a history of individual intolerance to amide anesthetics through selection of a comprehensive method of preventive intraoperative anesthesia for this category of patients. **Materials and methods.** Ninety females took part in the study. Clinical, laboratory, and mathematical and statistical research methods were used to study the preventive analgesic effectiveness of the compared methods of anesthesia. Five samples of biological material, called the control points, were taken: before surgery, immediately after it, then 1, 3 and 6 hours after intervention. In this way, an idea was got about the initial level of the studied indicators and their changes during the postoperative stay in the hospital. Properties of various combinations of propofol, ketamine, fentanyl, and dexketoprofen were studied. **Results.** It was revealed that a combination of propofol (2 mg/kg), fentanyl (0.1 µg/kg), ketamine (0.1 mg/kg), as well as additional intravenous administration of dexketoprofen (50 mg) at the stage of premedication has the advantages in terms of preventive intraoperative analgesia. Effectiveness of the proposed method of anesthesia was proved by significantly better indicators of vital functions (heart rate, mean arterial pressure) and serum levels of some laboratory markers of stress (glucose, cortisol, insulin, cortisol-insulin index). Differences in the studied parameters were recorded both when comparing them between the groups at the same control time points and considering the development and regression of the postoperative pain syndrome severity within the groups. **Conclusions.** The proposed method of anesthesia has a reliable advantage in terms of preventive reduction of the postoperative pain syndrome of UC in patients who cannot have application anesthesia due to individual intolerance to amide drugs. The specified method has a positive effect on vital functions and serum levels of some laboratory markers of stress, and the fastest recovery of patients is caused by a lower suppressive action of the anesthetic drugs used.

Keywords: uterine curettage; anesthesia; one-day gynecology

Today, an increasing number of doctors around the world prefer to manage patients according to the principles of outpatient approaches to treatment [1]. Such a tactic is absolutely justified, as it allows minimizing the time spent by the patient in the hospital, significantly reducing the costs

for medical care, reducing the risks of hospital-acquired infections and the impact of iatrogenic factors on health, improving the quality of life of patients, etc. [2]. If surgical intervention is required, outpatient medicine gives preference to minimally invasive surgery considering its less traumatic



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nature, possibility of early activation of patients, reduced risk of developing postoperative complications associated with the long stay of patients in a forced position, a decrease in the severity of postoperative pain syndrome and postoperative stress response. One-day gynecology is no exception [3]. One of the most common surgical interventions performed in patients of outpatient gynecological hospitals is uterine curettage (UC) [4, 5]. This manipulation has a number of clinical and diagnostic advantages: it makes it possible to effectively remove unwanted formations in the uterine cavity and cervical canal, to collect a sufficient amount of biological material for histological examination of the uterine pathology, to treat various proliferative diseases of the endometrium, to identify the cause of menstrual cycle disorders in women, etc. However, during UC, a damage to soft tissues, though small, still occurs, which, in turn, leads to development of postoperative pain syndrome. Therefore, the tasks of an anesthesiologist, who provides anesthetic support of UC, includes not only creation of the maximum protective intraoperative background, but also adequate prevention of the postoperative pain syndrome.

Earlier, the results of studies were published on importance of a rational anesthetic approach to conducting outpatient surgical interventions [6], as well as the effectiveness of preventive intraoperative analgesia techniques in the early postoperative period after UC [7]. The information contained in them indicates that the most effective injectable drug used in the anesthetic practice is bupivacaine, a local amide anesthetic. Expediency of using the method of preventive application anesthesia with bupivacaine solution, which consists in the intraoperative treatment of the wound surface formed in the uterine cavity after endometrium separation, was proven in terms of effectiveness as compared to the analgesic techniques through injection of drugs, positive effect on the quality of patients' life in the postoperative period, and the economic component. However, one of the criteria that limits the use of this method is a history of allergic reactions to amide drugs. This exception is absolutely justified, since the use of any medicinal product that cause allergies in a patient can lead to a life-threatening condition. In such a case, the potential risk of complications exceeds the expected benefit from the administered drug. The number of women who are allergic to amide anesthetics is not very high [8], but this is not a reason to deprive them of the right to receive quality medical care or to exclude them from the target group of scientific research. That is why a decision was made regarding the need to study possible anesthetic approaches to improve the quality of providing anesthetic support to such patients.

Purpose: to improve the quality of providing anesthetic care in the early postoperative period after UC to the patients with a history of individual intolerance to amide anesthetics through selection of a reasonable method of preventive intraoperative anesthesia.

Materials and methods

The study was conducted on the basis of the Gynecological Department of State Institution "Institute of Medical Radiology named after S.P. Hryhoriev of the National Academy

of Medical Sciences of Ukraine". Ninety female patients took part in the study. The scientific work was regulated by the requirements of the World Medical Association Declaration of Helsinki "Ethical principles for medical research involving human subjects" (revised in 2008). All patients gave informed consent to participate in the experiment [9]. The criteria for inclusion in the study were: informed consent to participate, anesthetic risk of ASA of no more than I–II, age from 21 to 55 years, the need to diagnose the state of the endometrium, a neoplasm of the uterine cavity or removal of its polyps. The exclusion criteria were as follows: the need for urgent intervention, acute inflammatory and ulcerative diseases of the gastrointestinal tract, other chronic diseases in the acute stage, a history of diabetes mellitus or hyperglycemia in the first blood test, eating during the day and during the study, breastfeeding, liver disease with impaired metabolic function, acute and chronic kidney damage of all stages. The patients did not have a confirmed allergy history, but its presence was assumed by default. Using the blind envelope method, all women were divided into 3 groups depending on the method of anesthesia. As to age and anthropometric parameters, there were no reliable differences between the groups of patients.

All study participants underwent catheterization of a peripheral vein with Vasofix Braunüle G18 intravenous catheter and intravenous premedication with atropine (0.01 mg/kg), diphenhydramine (0.15 mg/kg) and ondansetron (4 mg) 10 minutes before the start of surgery.

Group I (n = 32) included patients who were operated under intravenous anesthesia based on 1% propofol (2 mg/kg) and 5% ketamine (0.2 mg/kg); analgesia was performed with 0.005% fentanyl solution (0.2 µg/kg).

Group II (n = 26) consisted of women who underwent intravenous anesthesia with 1% propofol (2 mg/kg) and 5% ketamine (0.2 mg/kg); analgesia was performed with 0.005% fentanyl (0.2 µg/kg) and dexketoprofen at a dose of 50 mg. Dexketoprofen was administered as part of premedication immediately before the start of surgery.

Group III (n = 32) were patients who were operated under intravenous anesthesia with 1% propofol (2 mg/kg) and 5% ketamine (0.1 mg/kg); the analgesic component was represented by 0.005% fentanyl at a dose of 0.1 µg/kg and dexketoprofen in the mean therapeutic dose of 50 mg, which was additionally administered intravenously as part of premedication before surgery.

Local amide anesthetics were not used for preventive intraoperative anesthesia in any of the groups in the postoperative period, which made it possible to use the studied anesthesia schemes for patients allergic to these drugs.

The average duration of the surgical intervention was 7.0 ± 0.3 min in group I, 7.65 ± 0.20 min in group II, and 7.28 ± 0.30 min in group III ($p > 0.05$).

The main indicators of vital functions and biochemical markers of stress were the criteria for effectiveness of analgesia in the postoperative period. Among vital functions, oxygen concentrations in capillary vessels (SpO_2), heart rate (HR), systolic (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were investigated, and we chose glucose, insulin, blood cortisol, cortisol-insulin index (C/I) from the biochemical markers of stress. HR, SBP, DBP

and MAP were recorded with a surgical monitor UTAS-300. Serum levels of cortisol and insulin were measured by the enzyme-linked immunosorbent assay (ELISA) with reagent kits DSU-ELISA-Steroid-Cortisol (Ukraine) and Insulin-ELISA-BEST, respectively. The blood serum glucose level was evaluated by the calorimetric method. C/I was calculated according to the formula of L.E. Panin [10]:

$$C/I = \frac{C(\text{cortisol at the study stage}) \times 100 \% / C1(\text{cortisol before surgery})}{I(\text{insulin at the study stage}) \times 100 \% / I1(\text{insulin before surgery})}$$

Five blood samples were taken at the following control points (c.p.): before surgery (marking "1"), immediately after surgery (marking "2"), 1 hour after surgery (marking "3"), 3 hours after surgery (marking "4"), 6 hours after surgery (marking "5"). So, we gained an understanding of the baseline level of the studied indicators and their changes during the entire time of the patients' postoperative stay in the hospital.

Next, comparison of the studied indicators in dynamics was carried out, namely between c.p. 1–2, 1–3, 1–4, 1–5, 2–3, 2–4, 2–5, 3–4, 3–5, 4–5.

Statistical processing of the obtained data was carried out using the software program SPSS 19.0. Shapiro-Wilk test was used to check normality of feature values distribution. Quantitative and qualitative variables were used during the statistical analysis. Qualitative data were presented as percentages; quantitative — in the form of the mean and standard error of the mean ($M \pm m$). Student's t-test was used to compare quantitative indicators. The critical level of significance for testing statistical hypotheses in the study was taken to be equal to 0.05.

Results

While analyzing the dynamics of vital indicators, no informative changes in SpO₂, SBP and DBP were detected; therefore, they are not stated in the article for discussion.

HR and MAP, on the contrary, had statistically reliable differences between the groups at different stages of the study. The obtained results for the indicators that characterize the work of cardiac activity are given in Table 1.

Reliable differences in HR between the groups were revealed 1 hour after the end of the surgical intervention. After this time and until the end of the study, HR in patients of group III was significantly lower compared to those in groups I and II ($p < 0.05$).

Let us consider the dynamics of HR in detail. Statistically significant differences in HR were registered in groups I and II when comparing c.p. 1–2, in groups II and III when comparing c.p. 1–5, and in all studied groups when comparing c.p. 1–3, 1–4 and 2–3. The analysis of the registered data shows the postoperative analgesic advantage of the anesthesia method, which was used in group III. It is quite likely that the additional use of dexketoprofen at the premedication stage provided a sufficient analgesic effect in the initial stages of the postoperative period, and half doses of ketamine and fentanyl allowed the patients to recover the functional activity faster owing to a lower, compared to other drug combinations, neurodepressive effect.

When analyzing dynamics of blood pressure, differences in the analgesic effect of the investigated methods of anesthesia were revealed. Despite the fact that SBP and DBP did not change statistically significantly, MAP indicators were the response of blood pressure to postoperative stress. In the first three control points, the data differed significantly when comparing groups II and III. These differences were recorded immediately after completion of UC. At the end of the first postoperative hour, MAP indicators remained practically the same and had no reliable differences, and already 3 hours after the surgery and until the end of the observation, reliable differences were registered when comparing with group III.

Table 1. HR (bpm) and MAP (mm Hg) at the study stages

Indicator	Group I (n = 32)	Group II (n = 26)	Group III (n = 32)	p
HR 1	73.70 ± 1.13	73.30 ± 0.67	73.30 ± 1.03	> 0.05
HR 2	77.70 ± 1.03	76.30 ± 0.48	77.10 ± 0.71	> 0.05
HR 3	86.00 ± 0.97	85.50 ± 0.74	73.40 ± 0.88	$p_{I-III} < 0.001$ $p_{II-III} < 0.001$
HR 4	79.10 ± 0.94	78.50 ± 0.56	76.30 ± 0.79	$p_{I-III} < 0.05$ $p_{II-III} < 0.001$
HR 5	76.30 ± 0.94	73.40 ± 0.68	70.30 ± 0.94	$p_{I-III} < 0.001$ $p_{II-III} < 0.001$
MAP 1	93.10 ± 1.41	90.80 ± 0.75	91.20 ± 1.33	> 0.05
MAP 2	95.80 ± 0.77	95.00 ± 0.69	97.80 ± 0.91	$p_{II-III} < 0.05$
MAP 3	101.6 ± 0.9	103.10 ± 0.77	103.20 ± 0.98	> 0.05
MAP 4	99.00 ± 0.94	97.00 ± 0.73	92.70 ± 0.93	$p_{I-III} < 0.001$ $p_{II-III} < 0.001$
MAP 5	95.50 ± 1.09	91.90 ± 0.55	91.50 ± 1.16	$p_{I-II} < 0.01$ $p_{I-III} < 0.05$

Notes, hereinafter: $p > 0.05$ — no reliable differences between indicators of all groups; level of significance of differences: p_{I-II} — between groups I and II; p_{I-III} — groups I and III; p_{II-III} — groups II and III.

In all studied groups, MAP indicators differed significantly when comparing c.p. 1–3 and 2–3, and in groups I and II — when comparing c.p. 1–4. Changes in vital functions characterize the impact of the studied anesthesia methods on the course of postoperative pain syndrome. During the study, a complete return of indicators of the cardiovascular system functional activity to the initial level was recorded in group III. In groups I and II, this process was somewhat slowed down, which is probably due to the fact that the course of postoperative recovery was not as active as in patients who received a combination of dexketoprofen and half doses of drugs for anesthesia. This is probably caused by a smaller (dose-dependent) depressant effect of anesthetics on the central nervous system.

Both indicators described above (HR and MAP) comprehensively reflect the response of the cardiovascular system to the course of the postoperative period and demonstrated the influence of the investigated anesthesia methods on the recovery of patients. The analysis of HR and MAP show that the use of half doses of ketamine and fentanyl in combination with a therapeutic dose of dexketoprofen has a positive effect on the body's response to the postoperative stress, as well as to the stress during early period of recovery from UC.

Laboratory data are of some interest as a tool for objectifying the course of the postoperative period in patients of different groups. The obtained biochemical markers of stress confirm better analgesic efficiency of a combination of dexketoprofen and half doses of anesthetics compared to other methods of anesthesia.

The dynamics of glucose levels is shown in Fig. 1.

Glucose levels were significantly lower in patients of group III compared to those in groups I and II. Similar

to hemodynamic indicators, reliable differences appeared after the first hour of the postoperative period. Speaking about the dynamics of glycemia, it should be noted that in patients of group III, return of indicators to the baseline was registered earlier than in women of other studied groups.

With certain consideration of cortisol and insulin levels in the process of comparing them between the studied pairs of control points, no reliable differences were found. Significant changes were found only when determining the average dynamics (Δ) of serum levels of these hormones (Table 2).

Thus, an increase in the serum level of cortisol was significantly lower in patients of group III compared to other studied groups between c.p. 1–2, 2–3. The rate of decrease also testified to the effectiveness of the anesthetic technique in group III (it was higher in patients of group III than in group I when comparing c.p. 3–4).

When analyzing the rate of decrease in the insulin concentration, it was found that it differed significantly when comparing c.p. 1–2, and the rate of its increase — when comparing c.p. 3–4 in patients of group III with those of groups I and II. Although the obtained results are not of a systemic nature, they still indirectly confirm the expediency of the combined use of dexketoprofen with half doses of fentanyl and ketamine.

The results of C/I calculation as a generalizing characteristic of the hormonal response to postoperative stress confirmed clinical effectiveness of the anesthesia method used in group III.

Interestingly, it is the generalizing indicators of hemodynamic response (MAP) and hormonal stress response (C/I) that turned out to be informative. At the same time, SBP and DBP, cortisol and insulin, which characterize some components of these parameters, had

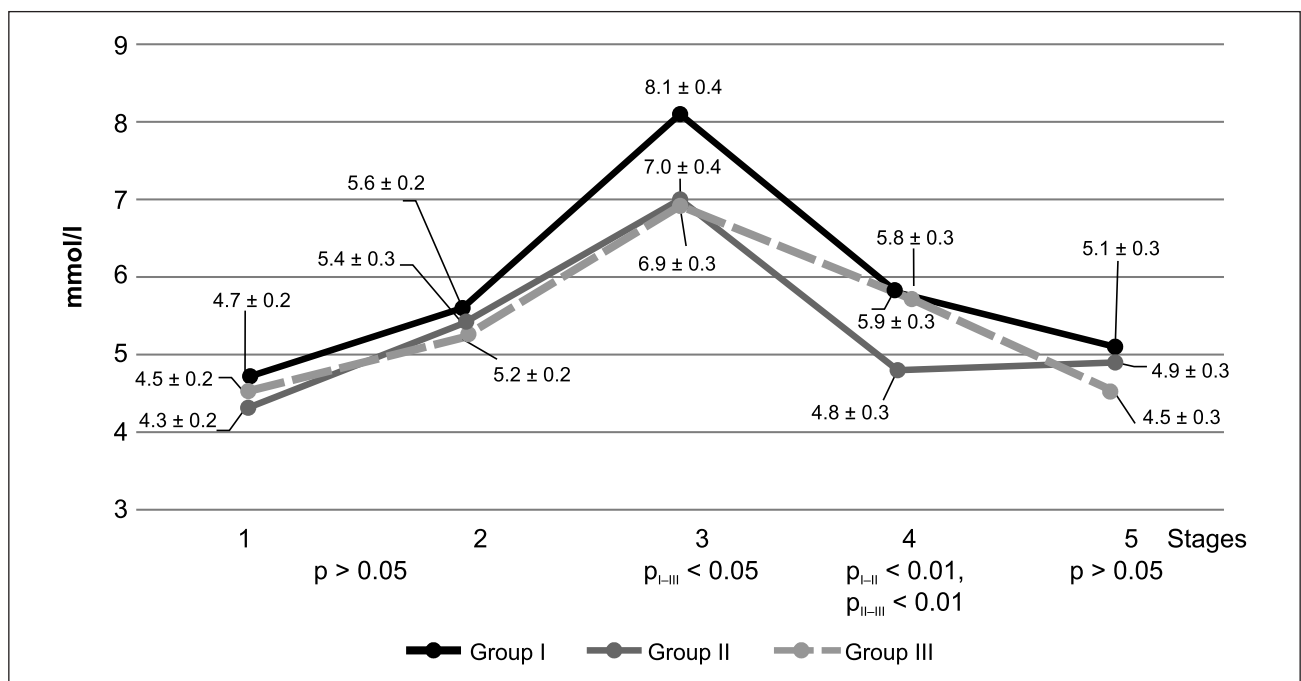


Figure 1. Dynamics of the glucose level (mmol/l) at different stages of the study

no reliable differences when comparing them between groups at the same control points.

The analysis of C/I revealed the advantage of a combination of non-steroidal anti-inflammatory drugs and half doses of drugs for anesthesia already at the beginning of the postoperative period. Reliable differences in C/I indicators occurred as early as in c.p. 2. The advantage was preserved practically throughout the whole observation period, with the exception of only c.p. 5.

Discussion

Therefore, taking into account the obtained results, the effectiveness of the method for preventive intraoperative anesthesia in the early postoperative period after UC becomes clear in patients who have individual intolerance to the amide anesthetics.

The levels of HR and MAP characterize the response of the cardiovascular system to surgical stress in general and to the postoperative pain syndrome in particular. Reliable differences in these indicators between the groups within

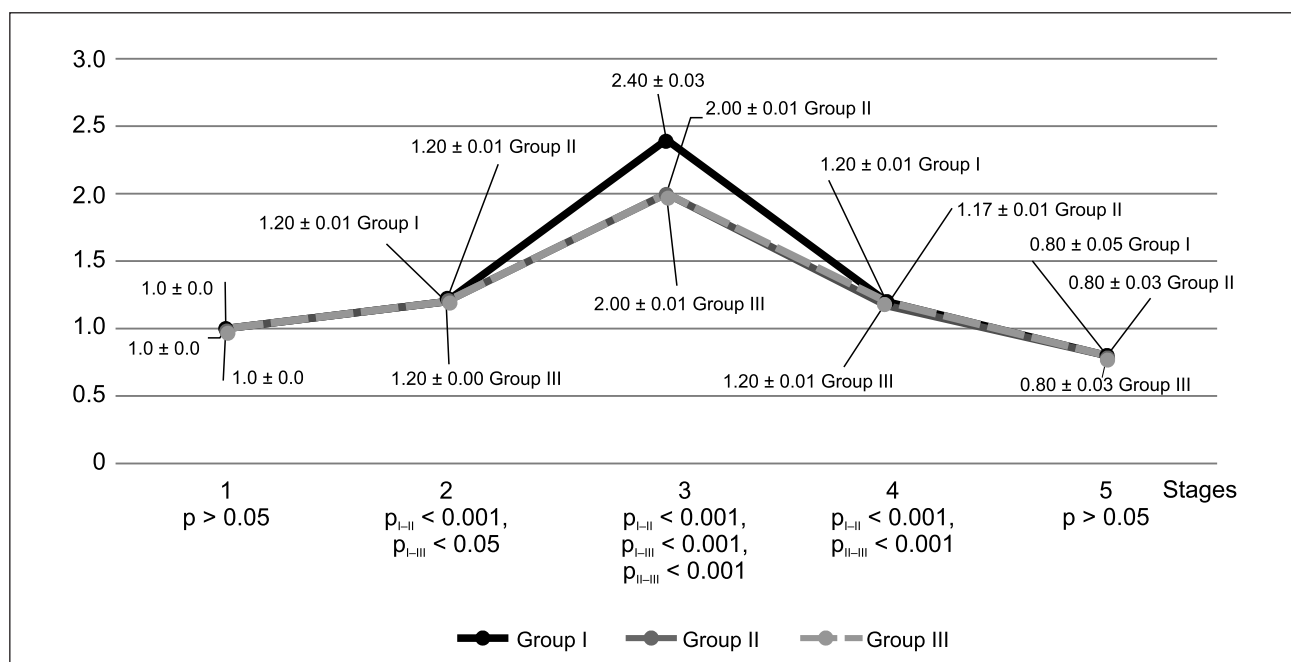


Figure 2. Dynamics of C/I at different stages of the study

Table 2. Average dynamics of cortisol (Δ) in the studied groups

Control points	Group I (n = 32)	Group II (n = 26)	Group III (n = 32)	p
<i>Insulin</i>				
1-2	+31.6	+22.5	+26.1	p _{I-II} < 0.01 p _{I-III} < 0.01 p _{II-III} < 0.05
2-3	+46.1	+39.1	+37.3	p _{I-II} < 0.05 p _{I-III} < 0.01
3-4	-114.0	-105.2	-98.4	p _{I-III} < 0.01
4-5	-103.0	-97.3	-102.6	> 0.05
1-5	-139.2	-140.9	-137.7	> 0.05
<i>Cortisol</i>				
1-2	-1.2	-1.1	-1.1	p _{I-II} < 0.01 p _{I-III} < 0.01 p _{II-III} < 0.01
2-3	-3.6	-3.9	-3.6	> 0.05
3-4	+2.6	+2.3	+2.0	p _{I-III} < 0.01 p _{II-III} < 0.05
4-5	+1.4	+1.2	+1.4	> 0.05
1-5	-0.8	-1.4	-1.2	> 0.05

the same control point, as well as their changes compared to different control points in the same groups indicate that the additional use of dexketoprofen at a dose of 50 mg at the premedication stage and the half dose of fentanyl (up to 0.1 µg/kg) and ketamine (up to 0.1 mg/kg) has a positive effect on the state of cardiac activity and vascular tone, which also proves the preventive effectiveness of given medicines in combating the consequences of surgical aggression in the early postoperative period.

Biochemical markers of stress — cortisol and insulin, or rather, their summative index, C/I — show similar results. Dynamics of this parameter indicate lower severity of the postoperative pain syndrome in patients who underwent anesthesiologic support for UC using the above combination. Reliability of statistical differences in C/I between groups in comparable control points testify in favor of group III, as they indicate a stronger protective effect of the anesthetic technique used in women of this group.

Summarizing the above, it should be stated that a combination of dexketoprofen and half doses of fentanyl and ketamine allows improving the quality of anesthetic support for patients who have individual intolerance to amide anesthetics, namely increasing the safety and effectiveness of anesthesia in the early postoperative period after UC and creating opportunity to conduct early prevention of the postoperative pain syndrome.

Conclusions

Based on the data obtained in the research and the results of their analysis, it is possible to conclude the following:

1. For patients who have individual intolerance to amide anesthetics, an alternative preventive method of anesthesia in the early postoperative period after UC is the use of a combination of dexketoprofen in the mean therapeutic dose (50 mg) at the premedication stage with propofol 2 mg/kg, fentanyl 0.1 µg/kg and ketamine 0.1 mg/mg.

2. The proposed method of anesthesia has a reliable advantage in case of preventive reduction of pain syndrome after UC in patients who cannot undergo application anesthesia due to individual intolerance to amide drugs. The specified method has a positive effect on vital functions, serum levels of some laboratory markers of stress and contributes to the fastest recovery of patients.

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Обґрунтування вибору методу превентивної інтраопераційної анестезії при вишкрібанні порожнини матки в пацієнок з індивідуальною непереносимістю амідних анестетиків

Резюме. Актуальність. Вишкрібання порожнини матки (ВПМ) широко використовується у світовій клінічній практиці з огляду на його велику діагностичну та лікувальну цінність. Однак ВПМ призводить до пошкодження цілісності м'яких тканин, спричиняючи розвиток післяопераційного болювого синдрому. Деякі пацієнтки мають індивідуальну непереносимість амідних анестетиків, що обмежує їх використання в цій когорті. **Мета роботи:** поліпшити якість надання анестезіологічної допомоги в ранньому післяопераційному періоді після ВПМ жінкам, які в анамнезі мають індивідуальну непереносимість анестетиків амідного ряду, шляхом вибору обґрунтованого методу превентивної інтраопераційної анестезії для такої категорії хворих. **Матеріали та методи.** У дослідженні взяли участь 90 жінок. Для вивчення превентивної анальгетичної ефективності порівнюваних типів анестезії були використані клінічні, лабораторні та математико-статистичні методи дослідження. Проведено 5 заборів біологічного матеріалу, названих контрольними точками: перед операцією, відразу після неї, а також через 1, 3 й 6 годин після втручання. У такий спосіб було отримано уявлення щодо вихідного рівня досліджуваних показників та їх змін упродовж післяопераційного перебування в стаціонарі. Вивчалися особливості різних комбінацій пропофолу, кетаміну, фентанілу, а також декскетопрофену. **Результати.** Виявлено,

що переваги превентивного інтраопераційного знеболювання має комбінація пропофолу (2 мг/кг), фентанілу (0,1 мкг/кг), кетаміну (0,1 мг/кг), а також додаткове внутрішньовенне введення декскетопрофену (50 мг) на етапі премедикації. Ефективність запропонованого методу анестезії доведена вірогідно кращими показниками вітальних функцій (частота серцевих скорочень, середній артеріальний тиск) і сироваткових рівнів деяких лабораторних маркерів стресу (глюкоза, кортизол, інсулін, кортизол-інсуліновий індекс). Відмінності досліджуваних параметрів зафіксовані як при їх порівнянні між групами в однакових контрольних часових точках, так і з огляду на динаміку й регресування інтенсивності післяопераційного болювого синдрому всередині груп. **Висновки.** Запропонований метод анестезії має вірогідну перевагу щодо превентивного зниження інтенсивності післяопераційного болювого синдрому ВПМ у пацієнок, у яких неможливо провести аплікаційну анестезію через індивідуальну непереносимість препаратів амідного ряду. Зазначений метод позитивно впливає на показники вітальних функцій і сироваткові рівні деяких лабораторних маркерів стресу, а якнайшвидше відновлення пацієнок зумовлено меншою пригнічувальною дією цих препаратів для наркозу.

Ключові слова: вишкрібання порожнини матки; анестезія; гінекологія одного дня