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The concentration of lidocaine in the blood after intravenous and epidural administration with extensive hepatic resections

The aim of the work: to identify the concentration of lidocaine in patients' blood during an extensive hepatic resection, with its intravenous and epidural administration in dynamics for intra- and postoperative analgesia, to evaluate its analgesic effect and toxicity potential.
Materials and Methods. The study included 27 patients, who underwent hepatic resection with preservation of 30–60 % of the parenchyma. For all patients, multicomponent intraoperative anesthesia was used. Depending on the adjuvant, patients were divided into two groups: the main group (group 1) consisted of 7 patients who received intravenous (IV) administration of lidocaine, and a comparison group of 20 patients (group 2) whose complex anesthesia was supplemented with thoracic epidural anesthesia (EDA).
To solve the tasks was to develop and validate a rapid, sensitive and robust method for the detection and quantification of lidocaine in human plasma using purification by coagulation and ultracentrifugation with cooling followed Liquid chromatography with Orbitrap HRMS method.
The method showed a dynamic linear range of 0.1 to 1000 ng/mL with a linearity expressed by the regression coefficient (R^2) and a value of 0.9947. The quantitation limit (LOQ) was found to be 1 ng/mL and the detection limit (LOD) 0.3 ng/mL. Recovery accuracy and repeatability were satisfactory. Finally, the method was applied to 54 real human plasma.
Results and Discussion. 2 hours after the surgery, there was a tendency (P = 0.29) for a higher concentration of lidocaine in the blood by 28.8 % after epidural administration of lidocaine compared with intravenous administration (1.84 μg/ml in group 1, 2.37 μg/ml – in group 2, p = 0.29), with no fundamental difference 14 hours after surgery (2.62 μg/ml and 2.85 μg/ml, p = 0.76). Epidural administration of the drug was also accompanied by a tendency to increase the frequency of hemodynamic disorders, which was reflected in an increase in the dose of norepinephrine, which was intended to correct blood circulation parameters, by 1.3 times (total dose in group 1 (158.4±58.1) ng, group 2 – (206.9±76.4) ng, p = 0.14). No life-threatening toxic reactions were noticed in any of the cases.
The use of lidocaine as an adjuvant for intra- and postoperative analgesia by intravenous and epidural administration with extensive hepatic resections, in most cases, does not lead to an increase of the drug compound in the blood higher than the generally accepted toxic content is. The content of the drug in the blood can be exceeded with epidural administration compared with intravenous administration. The analgesic effect of intravenous lidocaine is not lower than the epidural and may even last longer until the first administration of a narcotic analgesic after surgery for pain relief. However, epidural block is accompanied by intraoperative hemodynamic instability and an increase in the total dose of norepinephrine to correct blood circulation parameters.

Key words: complex anesthesia; lidocaine intravenous administration; extensive hepatic resection; pain syndrome.

Extensive hepatic resections are complex and traumatic operations. To potentiate the effectiveness of the traditional complex anesthesia with tracheal intubation, muscle relaxation and artificial lung ventilation, EDA of the surgical intervention zone is additionally used. Using such an approach is now regarded as the "gold standard" for pain relief of extensive hepatic resections. At the same time, in addition to the positive aspects (potentiation of intraoperative analgesia, the possibility of prolonged postoperative analgesia, improvement of the results of intensive postoperative therapy – rapid recovery of peristalsis, the possibility of an earlier start of enteral nutrition, a reducing the likelihood of respiratory failure, etc.) there is a number of negative effects (possibility of spinal block, epidural hematoma etc.). In addition, it is not always possible to implement EDA, as dysfunction of hemostasis with the risk of increased bleeding, which is often found in patients with hepatic pathology, are a contraindication for its implementation [1, 2]. Currently, alternative methods of potentiation of traditional complex anesthesia are being sought [3, 4]. One of these methods, which have attracted attention in recent years, is the intravenous administration of lidocaine [5–7]. The complexity of this approach to anesthesia lies in the fact that the liver is the main organ of the drug metabolism and its use may be accompanied by an increase in the likelihood of toxic reactions (mental disorders, convulsions, collapse and asystole). In the available literature, there are no data on the concentration of lidocaine in the blood during its intravenous administration for intra- and postoperative pain relief in extensive hepatic resections [8–10]. In addition, apart from that it is important to monitor the blood concentration of lidocaine when it is used for EDA, and how safe it is for patients with extensive hepatic resection, and if the analgesic effect of EDA is associated with the accumulation of local anesthetic in the blood.

The aim of the work: to identify the concentration of lidocaine in the blood during its intravenous and epidural administration in dynamics for intra- and

postoperative analgesia, to evaluate its analgesic effect and toxicity potential in patients during extensive hepatic resection.

Materials and Methods. The study included 37 patients, who have been done hepatic resection with various pathologies with preservation of 30–60 % of the parenchyma. In all cases, multicomponent anesthesia was used for intraoperative anesthesia. Depending on the adjuvant, the patients were divided into the main group (group 1) of intravenous administration of lidocaine and the comparison group (group 2) – EDA (Table 1). In the postoperative period, all patients received planned anesthesia: paracetamol up to 3g per day and dexketoprofen trometamol 50 mg three times a day, as well as, on request, an additional narcotic analgesic (fentanyl), assessing pain on a visual analog scale (VAS) of more than 4 points. The safety of anesthesia methods was assessed by the concentration of lidocaine in serum, which was determined by the original method.

To solve the tasks was to develop and validate a rapid, sensitive and robust method for the detection and quantification of lidocaine in human plasma using purification by coagulation and ultracentrifugation with cooling followed Liquid chromatography with Orbitrap HRMS method.

The method showed a dynamic linear range of 0.1 to 1000 ng/mL with a linearity expressed by the regression coefficient (R^2) and a value of 0.9947. The quantitation limit (LOQ) was found to be 1 ng/mL and the detection limit (LOD) 0.3 ng/mL. Recovery accuracy and repeatability were satisfactory. Finally, the method was applied to 54 real human plasma.

Description of the method for determining the concentration of lidocaine

The safety of the analgesic methods was also assessed by their effect on the cardiovascular system, the incidence of hypotension (mean arterial pressure ≤ 65 mm/Hg), the need to use vasopressors (norepinephrine) to maintain mean blood pressure (MAP) not lower than 65 mm/Hg and the frequency of toxicity of local anesthetics by clinical signs. Patients were under continuous invasive blood pressure (IBP) monitoring, non-invasive blood pressure (NIBP) monitoring, MAP, heart rate (HR) monitoring, respiratory rate (RR) monitoring, intraoperatively and in the intensive care unit (ICU) using patient's monitors Gamma and Gamma XL (Draeger Medical, Germany).

The effectiveness of intraoperative analgesia was assessed by hemodynamic parameters [20, 21, 22], the amount of fentanyl injected, and the time before the first dose of narcotic analgesic during the postoperative period. The effectiveness of pain relief after surgery was assessed by the data of the visual analogue scale and the sum of narcotic analgesics.

All of these results were recorded intraoperatively and in the first 5 days of the postoperative period, followed by statistical analysis of the descriptive method and quartile, the results of the descriptive analysis of quantitative parameters are given as estimates of the sample mean (Mean) and standard deviation (SD), as well as the median (Median), upper and lower quartile [Q1–Q3]. With symmetrical selection, a one-way ANOVA test was used to assess significance, the difference was considered statistically significant at $p<0.05$.

Table 1. Groups of patients according to the method of intra- and postoperative pain relief

	Group 1 (main)	Group 2 (comparison)
Number of the tested patients	7	20
Type of anesthesia	Endotracheal anesthesia + Sol. Phentanili 0.005% 0.8–3 μg/kg/h i/v + Rocuronium 0.15 μg/kg/h + inhalation anesthetic Sevoflurane (Minimum alveolar concentration (MAC) 0.7-0.9)	
Type of adjuvant intraoperatively	I/v lidocaine 1.5 % 1.5 μg/kg loading dose, 1 μg/kg maintenance dose, 0.7–1 μg/kg – continuous infusion for the next 24 hours after surgery	In the epidural space lidocaine 1.5 % 70–80 μg/h, in the postoperative period lidocaine 1.5 % 70–80 μg/h for 2–3 days
Planned anesthesia in the postoperative period	Paracetamol 3 g/day + dexketoprofen trometamol 50 mg 3 times a day	
Type of adjuvant after surgery	I/v lidocaine 1.5 % 0.7–1 μg/kg – continuous infusion for the next 24 hours	In the epidural space lidocaine 1.5 % 70–80 μg/h for 2–3 days

Results and Discussion. Patients of the selected groups did not differ in age, body mass index (BMI), reason for surgery, degree of anesthetic risk, duration and extent of operation (Table 2).

2 hours after the operation, there was a tendency (p = 0.29) to a higher concentration of lidocaine in the blood in the comparison group (group 2), where it was 2.37 μg/ml, while in the main group (group 1) it was 1.84 μg/ml (Fig.1). Consequently, according to studies, the concentration of lidocaine in the blood during epidural anesthesia is 1.3 times higher than the content of the drug compared to intravenous administration in both groups, there were cases when the concentration of lidocaine in the blood exceeded the generally accepted toxic level of 5.0 μg/ml [14]: in the main group – in 2 patients (5.27 μg/ml and 6.73 μg/ml), in the comparison group – in 1 patient (6.29 μg/ml). The content of lidocaine 14 hours after the surgery in the selected groups almost did not differ (2.62 in the main group, 2.85 in the comparison group) (see Fig.1).

Epidural anesthesia intraoperatively (comparison group) was accompanied by a higher incidence of hemodynamic instability, which was reflected in an increase in the frequency of prescribing a sympathomimetic (norepinephrine) to correct blood circulation parameters. The total dose of the norepinephrine in the comparison group was 1.3 times higher than that in the main group (total average (206.9±76.4) ng and (158.4±58.1) ng, respectively, p=0.14) (Fig.2). Increasing the dose of the specified sympathomimetic in patients of the group 2 is with the development of a sympathetic block as a result of epidural anesthesia, which affects cardiac output and peripheral perfusion and leads to a decrease in blood pressure.

Table 2. Preoperative characteristics of the patients

Preoperative factors	I/v lidocaine (n = 7) – Group 1	Epidural anesthesia (n = 20) – Group 2	p value
Age, years, mean (SD)	54.6 (± 2.8)	48.2 (± 4.8)	0.07
Gender, n (%) Male Female	 1 (14 %) 6 (86 %)	 7 (35 %) 13 (65 %)	0.82
IMT, (kg/m2), mean (SD)	27.6 (± 7.2)	25.5 (± 4.7)	0.41
American society of anesthesiologists (ASA), n (%)	II – 6 (86 %) III – 1 (14 %)	II – 15 (75 %) III – 5 (25 %)	0.78
Causes of surgery	Benign disease – 2 (28 %) Malignant disease – 5 (72 %)	Benign disease – 4 (20 %) Malignant disease – 16 (80 %)	0.54
Operative time, min, mean (SD)	418.3 (± 137.5)	475.5 (± 201.4)	0.71

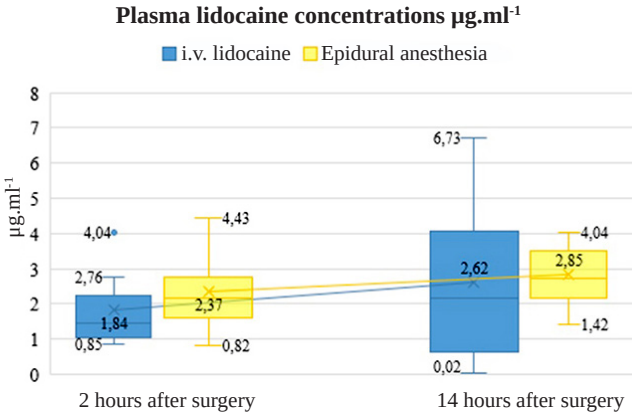

Fig. 1. Plasma lidocaine concentrations μg.ml^{-1}

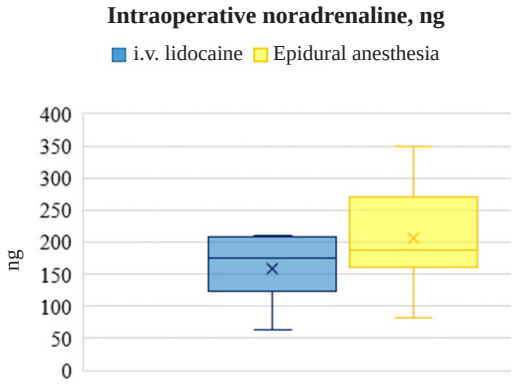

Fig. 2. Sum of intraoperative noradrenaline, ng

As a result of this therapeutic approach, there was no fundamental difference between the studied indications of intraoperative blood circulation (MAP, HR) between the groups (Table 3).

On the first day after surgery, the average daily value of the intensity of the pain syndrome according to the visual analogue scale in patients of group 1 was (4.4±1.1), of group 2 – (5.05±2.0) (Pic. 3), without a fundamental difference between the groups (p=0.48). The subsequent dynamics within 2–6 days after the surgery is shown in Fig. 3. This is explained by the cessation of intravenous administration and the preservation of epidural administration of in group 2.

There was a tendency (P=0.28) to extend the time before the first dose of narcotic analgesic after surgery in selected group 1 by 9.0 % (313.5±128.9) min in group 1, (287.7±101.6) min – group 2). In both groups, the degree of toxic reactions was insignificant – 1 patient of group 1 and 2 patients of group 2complained of nausea (which could also be due to the influence of other factors). Convulsions, cardiac arrest, mental disorders were not observed.

The parameters of changes in HR, RR and MAP as indicators of effectiveness with a sufficient amount of anesthetic in the period of 1–5 p/o days are shown in figures 4, 5, 6. There is no significant difference between the last indications, which further confirms the safety and effectiveness of this technique.

Table 3. Intraoperative characteristics (MAP, HR)

Factors	I/v lidocaine (n=7) – group 1	Epidural anesthesia (n=20) – group 2	p value
MAP (mmHg)	85 (± 14.3)	78 (± 12.6)	0.26
HR (per 1 min)	82 (± 11)	80 (± 12)	0.91

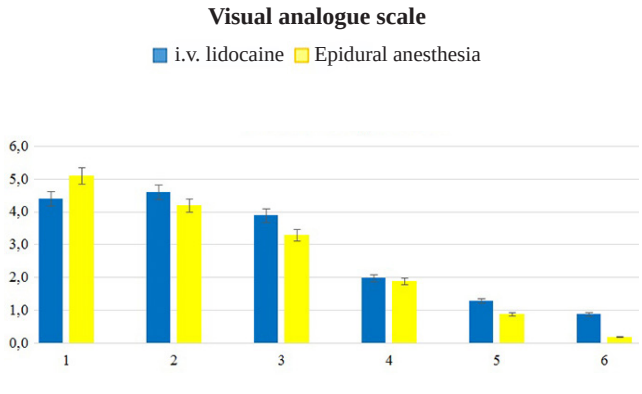

Fig. 3. Pain intensity on a visual analogue scale (VAS).

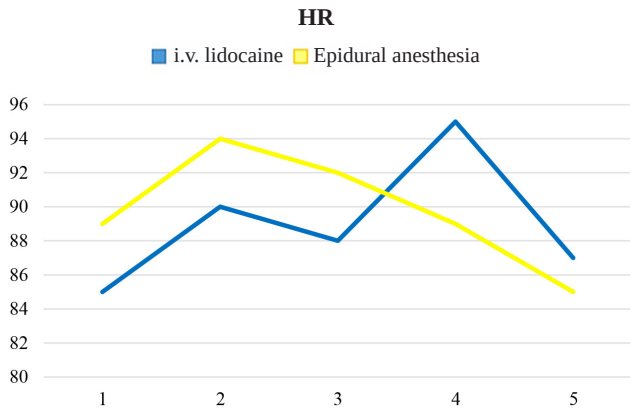

Fig. 4. Dynamics of HR change in the p/o period.

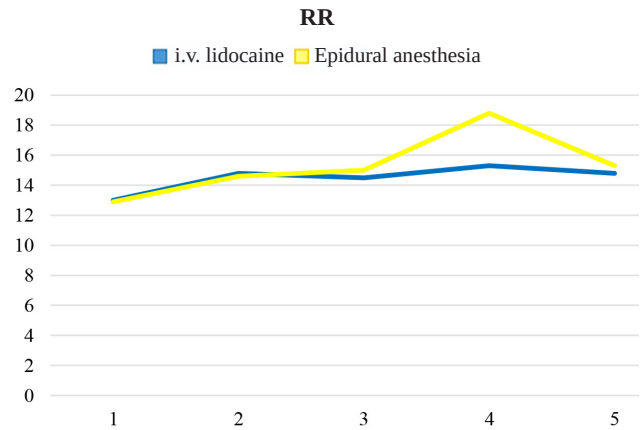

Fig. 5. Dynamics of change in RR in the p/o period.

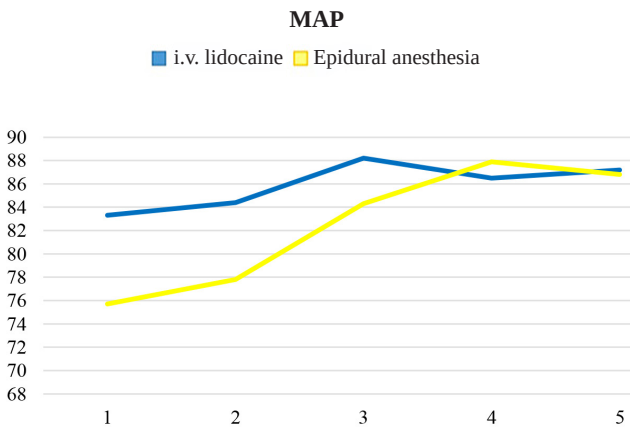

Fig. 6. Dynamics of change in MAP in the p/o period.

Discussion. In modern medical practice, extensive hepatic resection has become a routine treatment for certain liver diseases, such as primary or secondary malignancies. Pain syndrome during and after hepatic resection is intense, multifactorial, and occurs as a result of trauma from the surgical intervention itself (skin incision and muscle transection), significant dissection of internal organs, mobilization of the vascular bed of the liver, and often due to the presence of blood or other fluid accumulations in the abdominal cavity during the postoperative period. To potentiate commonly used multicomponent anesthesia in many cases epidural anesthesia is used, which has become to a certain extent the "gold standard" for these types of surgical intervention. However, it can be accompanied by a number of negative effects and cannot always be used due to the presence of contraindications as a result of liver dysfunction. This explains the search for an additional method of pain relief potentiation. Among which are the intravenous administration of lidocaine. However, the liver is the main organ of drug metabolism and its use can lead to toxic effects.

Our study conducted using the original method to determine the concentration of lidocaine in the blood, it was recorded that the content of the drug during intravenous administration of the drug in most cases does not exceed the generally accepted toxic concentration, and even when the dose is exceeded, it is not accompanied by dangerous clinical toxic manifestations.

According to the studies, the use of the original method for determining the concentration of lidocaine in the blood showed that the content of the drug during intravenous administration of the drug in most cases does not exceed the generally accepted toxic concentration, and even when the concentration is exceeded, it is not accompanied by dangerous clinical toxic manifestations. What is more, the concentration of the drug in the blood when using the "gold standard" of additional anesthesia for extensive liver resections was 1.3 times higher. In our opinion, this is due to the creation of a depot of lidocaine in the epidural space with a further slower entry into the bloodstream. In addition to the above, the accumulation of lidocaine in the epidural space is accompanied by an additional sympathetic block, which leads to a higher incidence of intraoperative hypotension, which in turn requires an increase in the frequency of administration and the total dose of sympathomimetic (according to studies of an increase in the total intraoperative dose of norepinephrine by 1.3).

The method used for the intravenous administration of lidocaine is accompanied by a level of pain relief that is not lower than epidural anesthesia, and possibly even exceeds it. This was reflected in the increase in the time to the first dose of narcotic analgesic after surgery by 1.3 times and the absence of a significant difference in the manifestations of pain syndrome according to the VAS.

According to other data studied, there was no fundamental difference between the methods of potentiation of intra- and postoperative pain relief.

Given the fact that there is the lack of data and literature on this issue, and there is the small number of patients to who this proposed analgesia technique was used, this issue requires further validation.

Conclusions. The use of lidocaine as an adjuvant for intra- and postoperative analgesia by intravenous and epidural administration, despite extensive hepatic resection, where the main metabolism of the drug occurs, in most cases does not lead to an increase of the drug in the blood above the generally accepted toxic level. However, the possibility of increasing the upper limit of the concentration of the drug in the blood requires careful monitoring of the patient's condition.

With epidural administration, the concentration of lidocaine may be higher than with intravenous administration (in 1.3 times). This fact requires further confirmation. Therefore, the positive balance between the rate of entry of lidocaine into the blood and the elimination of the drug from the blood during its epidural administration is no less. This explains that during extensive hepatic resection, the analgesic effect of epidural administration of lidocaine is associated not only with epidural analgesia, but also with the accumulation of lidocaine in the blood.

The analgesic effect of intravenous administration of lidocaine is not lower than that of the epidural and may even be accompanied by an increased interval until the first administration of a narcotic analgesic after surgery for pain relief.

The study took into account the fact that the epidural block is accompanied by intraoperative hemodynamic disorders, that was reflected in an increase in the total dose of norepinephrine to correct blood circulation parameters in 1.3 times, which is an additional invasive and dangerous intervention against the background of disorders of the hemostasis system, which confirms the advantage of the intravenous method drug administration. That’s why it is necessary to take into account the possibility of a short-term increase in pain intensity on the 2nd–3rd day after surgery after the cessation of intravenous administration of lidocaine.

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КОНЦЕНТРАЦІЯ ЛІДОКАЇНУ В КРОВІ ПРИ ВНУТРІШНЬОВЕННОМУ ТА ЕПІДУРАЛЬНОМУ ВВЕДЕННІ ПРИ ОБШИРНИХ РЕЗЕКЦІЯХ ПЕЧІНКИ

Мета роботи: визначити концентрацію лідокаїну у хворих, яким виконують обширну резекцію печінки, в крові при його внутрішньовенному та епідуральному введенні в динаміці для інтра- та післяопераційного знеболення, оцінити його знеболювальний ефект та потенціал токсичності.

Матеріали і методи. В дослідження включили 27 пацієнтів, яким було виконано резекцію печінки зі збереженням 30 – 60 % паренхіми. У всіх хворих для знеболення використовували багатокомпонентне інтраопераційне знеболення. Залежно від ад'юванту хворих розділили на дві групи: основну групу (1 група) склали 7 пацієнтів, у яких було застосовано внутрішньовенне (в/в) введення лідокаїну, та групу порівняння – 20 пацієнтів (2 група), які отримували класичну багатокомпонентну анестезію з доповненням торакальною епідуральною анестезією.

Для досягнення мети був розроблений та валідований швидкий, чутливий та надійний метод виявлення та кількісного визначення лідокаїну в плазмі з використанням очищення за допомогою коагуляції та ультрацентрифугуванням при температурі 4 °С з подальшим кількісним визначенням методом BEPX Orbitrap HRMS.

Метод показав динамічний лінійний діапазон від 0,1 до 1000 нг/мл з лінійністю, вираженою коефіцієнтом регресії (R2) 0,9947. Встановлено, що межа кількісного визначення (LOQ) становить 1 нг/мл, а межа виявлення (LOD) – 0,3 нг/мл. Точність відновлення та відтворюваність були задовільні. Розроблений метод був застосований до 54 реальних зразків плазми.

Результати досліджень та їх обговорення. Через 2 години після операції спостерігали (P=0,29) підвищення концентрації лідокаїну в крові на 28,8 % після епідурального введення лідокаїну порівняно з внутрішньовенним (1,84 мкг/мл у 1 групі, 2,37 мкг/мл – у 2 групі, p = 0,29), без достовірної різниці через 14 годин після операції (2,62 мкг/мл та 2,85 мкг/мл, відповідно, p = 0,76). Епідуральне введення препарату також супроводжувалося тенденцією до збільшення частоти гемодинамічних розладів, що відобразилося у збільшенні дози норадреналіну, призначеної для корекції параметрів кровообігу, в 1,3 раза (загальна доза в 1 групі 158,4 ± 58,1 нг, у 2 групі – 206,9 ± 76,4 нг, p = 0,14). У жодному випадку не спостерігали жодних загрозливих для життя токсичних реакцій.

Застосування лідокаїну як допоміжного засобу для інтра- та післяопераційного знеболення шляхом внутрішньовенного та епідурального введення при обширних резекціях печінки здебільшого не призводить до підвищення вмісту препарату в крові вище загальноприйнятого токсичного вмісту. Вміст препарату в крові може бути вищий при епідуральному введенні порівняно з внутрішньовенним. Знеболювальний ефект внутрішньовенного введення лідокаїну не нижчий, ніж при епідуральній анестезії, і навіть може подовжувати тривалість до першого введення наркотичного анальгетика після операції для знеболення. Водночас епідуральна блокада супроводжується інтраопераційною нестабільністю гемодинаміки та збільшенням загальної дози норадреналіну для корекції параметрів кровообігу.

Ключові слова: багатокомпонентна анестезія; внутрішньовенне введення лідокаїну; обширна резекція печінки; больовий синдром.