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OPTIMIZING EFFECTS OF MEGLUMINE SODIUM SUCCINATE “REAMBERIN” REGARDING POSTOPERATIVE ANESTHESIA IN BURNED PATIENTS AFTER SURGICAL NECRECTOMY

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Abstract. Introduction. Succinates (succinic acid and its salts) in the body are closely related to the “production” of energy, which is necessary for vital activity, since they are products of the fifth and substrate of the sixth reaction in the Krebs cycle. A possible way to improve tissue oxygenation without aggressive oxygen insufflation may be to improve the oxidative phosphorylation process. This pathway can be achieved through the use of succinates. **The purpose of the study.** To conduct a comparative study of the effect of meglumine sodium succinate and the level of tissue oxygenation in burned patients on the quality of postoperative anesthesia. **Materials and methods.** In this study, 106 patients aged 20 to 90 years after surgical necrectomy were examined and divided into two groups. The study was conducted in the Department of Thermal Injuries of the St. Petersburg Scientific Research Institute of Emergency Medicine named after I.I. Dzhanelidze. The amount of analgesics required for effective postoperative anesthesia (3 days) was determined in two groups of patients: those who received oxygen-air mixture insufflation as part of intensive care in the postoperative period (56 people) and additionally received reamberin infusion against the background of oxygen-air mixture insufflation (50 people). The number of postoperative complications was calculated according to the Clavien–Dindo classification of surgical complications. The parameters of oxygen metabolism were determined: saturation of hemoglobin with oxygen in arterial and venous blood, oxygen utilization coefficient by tissues. **Results.** Our proposed method of administration of the drug meglumine sodium succinate “Reamberin” intravenously drip burned in the postoperative period allowed to reduce the frequency of surgical postoperative complications by 31% according to Clavien–Dindo ($p < 0.05$), and also increases the utilization of oxygen by tissues in the area of the postoperative wound. The total number of opioid analgesics needed for complete relief of pain syndrome was 4 times less. **Conclusion.** Intravenous administration of meglumine sodium succinate “Reamberin” to those burned in the postoperative period made it possible to increase oxygen utilization by tissues in the area of the postoperative wound and reduce the frequency of surgical complications and the number of opioid analgesics.

Keywords: postoperative period, burns, pain relief, oxygen exchange, FiO_2 , meglumine sodium succinate “Reamberin”, surgical necrectomy



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ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ ПРЕПАРАТА МЕГЛЮМИНА НАТРИЯ СУКЦИНАТА «РЕАМБЕРИН» ДЛЯ ОПТИМИЗАЦИИ ПОСЛЕОПЕРАЦИОННОГО ОБЕЗБОЛИВАНИЯ ОБОЖЖЕННЫХ ПОСЛЕ ХИРУРГИЧЕСКИХ НЕКРЭКТОМИЙ

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Резюме. Введение. Сукцинаты (янтарная кислота и ее соли) в организме тесно связаны с «производством» энергии, которая необходима для обеспечения жизнедеятельности, так как они являются продуктами пятой и субстратом шестой реакции в цикле Кребса. Возможным путем улучшения оксигенации тканей без агрессивной инсuffляции кислорода может быть улучшение процесса окислительного фосфорилирования. Этот путь может быть достигнут за счет использования сукцинатов. **Цель исследования** — провести сравнительное изучение влияния меглюмина натрия сукцината «Реамберин» и уровня оксигенации тканей у обожженных на качество послеоперационного обезболивания. **Материалы и методы.** В данной работе обследовано 106 пациентов после выполненных хирургических некрэктомий в возрасте от 20 до 90 лет, которые были разделены на две группы. Исследование проводилось в отделе термических поражений ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи им. И.И. Джанелидзе». Определяли количество анальгетиков, необходимое для эффективного послеоперационного обезболивания (3 суток) у двух групп пациентов: получавших в составе интенсивной терапии в послеоперационном периоде инсuffляцию кислородно-воздушной смеси (56 человек) и дополнительно получавших инфузию Реамберина на фоне инсuffляции также кислородно-воздушной смеси (50 человек). Количество послеоперационных осложнений рассчитывали по классификации хирургических осложнений Клавье́на–Диндо. Определяли показатели кислородного обмена: насыщение гемоглобина кислородом артериальной и венозной крови, коэффициент утилизации кислорода тканями. **Результаты.** Предложенный нами способ введения препарата меглюмина натрия сукцината «Реамберин» внутривенно капельно обожженным в послеоперационном периоде позволяет снизить частоту хирургических послеоперационных осложнений на 31% по Клавье́ну–Диндо ($p < 0,05$), а также повышает утилизацию кислорода тканями в области послеоперационной раны. Общее количество опиоидных анальгетиков, необходимых для полноценного купирования болевого синдрома, было в 4 раза меньше. **Вывод.** Внутривенное назначение меглюмина натрия сукцината «Реамберин» обожженным в послеоперационном периоде позволило повысить утилизацию кислорода тканями в области послеоперационной раны и снизить частоту хирургических осложнений и количество опиоидных анальгетиков.

Ключевые слова: послеоперационный период, обожженные, обезболивание, кислородный обмен, FiO_2 , меглюмина натрия сукцинат «Реамберин», хирургическая некрэктомия

INTRODUCTION

Adequate pain relief during surgical procedures and the early postoperative period is one of the most important issues both for patients and for surgeons, pathophysiologists, anesthesiologists, intensive care specialists, pain physicians [8].

Intense postoperative pain syndrome (IPPS) causes spasm of microcirculatory bloodstream due to hypersecretion of catecholamines, which impairs tissue oxygenation and increases the frequency of postoperative surgical complications in burn patients [1–3]. Improving tissue oxygenation in the postoperative period through aggressive oxygen insufflation facilitates optimal postoperative pain relief in burn patients [3] and reduces the frequency of postoperative complications. The use of aggressive oxygen therapy to improve tissue oxygenation also has its negative properties, namely: lung complications increase due to damage to bronchiole surfactant system caused by high doses of oxygen [12, 15]. A possible way to improve tissue oxygenation without aggressive oxygen insufflation may be the improvement of oxidative phosphorylation, which promotes faster compensatory electron transfer in the respiratory chain complex and increases the functional activity of organelles in the synthesis of adenosine triphosphate (ATP). It might be achieved by using succinates [4, 5]. Succinates probably do not even improve oxygen transport directly. However, under conditions of hypoxia, succinate-oxidase oxidation ensures the preservation of *aerobic* energy production and normalizes oxygen transport and transmembrane transfer in conditions of both excess and deficiency [4, 5]. This improves tissue regeneration processes [6] and may contribute to a reduced need for postoperative pain relief in burn patients. However, no similar studies have been found, suggesting the possible use of succinates to increase the activity of opioid receptors and, consequently, to optimize postoperative pain relief in burn patients by reducing the use of opioids. There is only indirect evidence that succinate administration reduces the intensity of burning pain in patients with diabetic neuropathy [7].

AIM

The aim of the study was to conduct a comparative analysis of sodium succinate meglumine and tissue oxygenation levels in burn patients in terms of postoperative pain relief.

MATERIALS AND METHODS

A total of 106 patients aged 20 to 90 years (mean age 51.4 ± 2.1 years) were examined. The ratio of women to men was 1:1.46. All patients underwent surgery (surgical necrec-

tomy covering an area of 5 to 10%, with an average of 7%) under total intravenous anesthesia with tracheal intubation and artificial lung ventilation. The intensity of postoperative pain was assessed using a 10-point visual analog scale (VAS) and an inspiratory spirometer [13]. The number of opioid analgesics in mg per day required for adequate postoperative pain relief was calculated.

The percentage frequency of complications was assessed on the third day of the postoperative period using the Clavain–Dindo classification of surgical complications [14, 15].

Patients were divided into two groups: group 1 (56 patients) received insufflation of an air mixture containing 30% oxygen through binasal cannulas during the first two days of the postoperative period as part of complex therapy. The second group of patients (50 people) received intravenous infusion of 400 ml of the drug sodium succinate meglumine “Reamberin” during the first three days of the postoperative period as part of complex therapy, including insufflation of an air-oxygen mixture containing 30% oxygen.

Tissue oxygenation was assessed using the following techniques [16]: pulse oximetry, which allows determining the degree of oxygen saturation of arterialized blood, reflecting oxygen delivery to tissues ($SpO_2\%$), and cerebral/somatic oximetry, which allows assessing the degree of oxygen saturation of venous blood hemoglobin ($rSO_2\%$). The difference between $SpO_2\%$ and $rSO_2\%$ reflects the tissue oxygen utilization coefficient ($KuO_2\%$). Cerebral/somatic oximeter electrodes were placed on the damaged skin areas parallel to the surgical suture line, 3–5 cm away from it.

Statistical methods: the STATISTICA 6.0 statistical software package was used, as well as nonparametric statistical methods: median and 25–75% interquartile range. Changes in indicators within groups were determined using the Friedman, Wilcoxon, and Signs criteria. Differences in indicators between groups were determined using the Mann–Whitney U test. Percentages were compared using a four-field table of conjugate frequencies. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Table 1 shows the dynamics of studied indicators in the first group of patients who received insufflation of a 30% oxygen-air mixture during the first two days of the postoperative period. The administration of sodium succinate meglumine “Reamberin” in the postoperative period in patients with burns after surgical interventions (surgical necrectomies) increases oxygen utilization by tissues in the area of a surgical wound.

The results presented in Table 1 allow us to conclude that hemoglobin oxygen saturation in arterial blood



Table 1

Patients receiving insufflation of oxygen-air mixture 30%

Таблица 1

Пациенты, получавшие инсуффляцию кислородно-воздушной смеси 30%

Время фиксации / Time of fixation	Анализируемые параметры (M±m) / Analyzed parameters (M±m)				
	SpO ₂ %	rSO ₂ %	KuO ₂ %	Частота осложнений, % / The frequency of complications, %	Количество доз анальгетиков / Number of doses of analgesics
Сразу после операции / Immediately after the operation	94,5±0,2	78,4±0,2	18,3±0,2	–	–
1-е сутки / 1 day	96,3±0,2*	77,0±0,5*	19,7±0,4*	–	3,6±0,1
2-е сутки / 2 day	97,1±0,3*	74,4±0,6*	22,6±0,7*	–	1,4±0,2
3-и сутки / 3 day	98,2±0,2**	72,3±0,7*	24,7±0,7*	11	0,8±0,1
Итого / Total	–	–	–	11	5,6±0,3

Note: * p < 0,05; ** p < 0,001 relative to the value fixed immediately after the operation.

Примечание: * p < 0,05; ** p < 0,001 по отношению к величине, фиксированной сразу после операции.

Table 2

Patients who received an infusion of meglumine sodium succinate "Reamberin" in the postoperative period

Таблица 2

Пациенты, получавшие в послеоперационном периоде инфузию меглюмина натрия сукцината «Реамберин»

Время фиксации / Time of fixation	Анализируемые параметры (M±m) / Analyzed parameters (M±m)				
	SpO ₂ %	rSO ₂ %	KuO ₂ %	Частота осложнений, % / The frequency of complications, %	Количество доз анальгетиков / Number of doses of analgesics
Сразу после операции / Immediately after the operation	95,2±0,2	78,3±0,2	17,8±0,2	–	–
1-е сутки / 1 day	95,9±0,2	72,2±0,5*	24,7±0,4*	–	3,2±0,2
2-е сутки / 2 day	97,3±0,3*	71,1±0,6**	25,6±0,7**	–	0,8±0,1
3-и сутки / 3 day	98,0±0,2*	69,2±0,7**	27,5±0,7**	7,1	–
Итого / Total	–	–	–	7,1^	1,4±0,1^

Note: * p < 0,05; ** p < 0,001 relative to the value fixed immediately after surgery; ^ p < 0,05 relative to group 1 patients.

Примечание: * p < 0,05; ** p < 0,001 по отношению к величине, фиксированной сразу после операции; ^ p < 0,05 по отношению к пациентам 1-й группы.

increases statistically significantly from the moment of surgery to three days after surgery. At the same time, there is a statistically significant decrease in venous blood hemoglobin saturation. As a result, the oxygen utilization coefficient of tissues increases, although on the third day it remains below the physiological limit (25%).

On the third day, the severity index of complications according to the Clavien-Dindo classification of surgical complications was 11%; according to the degree of severity, 9.9% of complications were classified as grade I and 1.1% as grade II.

Throughout all three follow-up days, patients in group 1 required the prescription of opioid analgesics in decreasing manner.

Patients in group 2, who received additional infusion of the drug sodium succinate meglumine "Reamberin" in the intensive care unit during the postoperative period, are summarized in Table 2.

Group 2 showed an increase in oxygen saturation of arterialized blood hemoglobin, as well as a significant decrease in oxygen saturation of venous blood hemoglobin

from the first day, which led to a significant increase in tissue oxygen utilization within physiological limits.

The frequency of postoperative surgical complications in patients in group 2 was 7.1%, which is 31% lower ($p < 0.05$) than in patients in group 1. In terms of severity, the complications recorded in patients in group 2 were classified as grade I.

The data in Table 2 show that patients in group 2 required opioids on the first and second days. The total amount of opioid analgesics required for complete postoperative pain relief in group 2 was 4 times less than in group 1.

There is an active search for methods to reduce the use of opioid analgesics for postoperative pain relief [8, 15]. It has been established that improved tissue oxygenation in the postoperative period facilitates optimal postoperative pain relief for burn patients. The presence of hypoxemia and hypoxia reduces the sensitivity of opioid receptors, which requires an increased use of opioids. We adopted the working hypothesis that it is necessary to increase tissue oxygenation in the postoperative period in burn patients to optimize postoperative pain relief. A classic method of increasing oxygenation was implemented, which involved administration of oxygen-air mixture insufflation, and a second method was employed to enhance oxygen utilization by tissues through the improvement of oxidative phosphorylation, which facilitates faster compensatory electron transfer in the respiratory chain complex, increases the functional activity of organelles in ATP synthesis, and increases oxygen utilization by tissues by using sodium succinate meglumine "Reamberin" [4, 5, 10]. It has been established that there is a more pronounced increase in oxygen utilization by tissues under the influence of succinates, which ultimately contributes to a 4-fold reduction in opioid analgesics to control postoperative pain syndrome within three days. Mu-opioid receptors become more sensitive when succinates are present. Moreover, some researches show that succinates make insulin receptors more sensitive, which makes insulin therapy easier for people with diabetes [7].

At the same time, it has been established that the use of sodium succinate meglumine "Reamberin" in burn patients in the postoperative period contributes to a 31% reduction in the frequency of postoperative surgical complications, which can be explained by improved tissue oxygenation in the area of a surgical wound. Some studies also note that succinates can help wounds heal faster after surgery. Consequently, the use of sodium succinate meglumine "Reamberin" in burn patients in the postoperative period is justified both for optimizing pain relief and for reducing postoperative complications through tissue regeneration.

CONCLUSIONS

1. The administration of sodium succinate meglumine in burn patients soon after surgery (surgical necrectomies) increases oxygen utilization by tissues in a surgical wound.

2. When meglumine sodium succinate is prescribed during the first three days after surgical necrectomies, there is a fourfold decrease in the amount of opioid analgesics required for adequate postoperative pain relief, and a 31% reduction in the frequency of surgical complications according to Clavien–Dindo.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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