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**EFFECT OF INTRAVENOUS
INTRAOPERATIVE VERSUS
POSOPERATIVE PARACETAMOL
ON POSTOPERATIVE NAUSEA AND
VOMITING IN PATIENTS WITH MORBID
OBESITY UNDERGOING
LAPAROSCOPIC BARIATRIC SURGERY**

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Summary

Objectives: This randomized study aimed to compare the efficacy of intraoperative versus postoperative paracetamol on postoperative nausea and vomiting (PONV) in morbidly obese patients undergoing laparoscopic bariatric surgery.

Methods: Sixty patients were randomly divided into two equal groups (n=30). In the intraoperative paracetamol group, patients received intravenous (IV) infusion of paracetamol 1000 mg during anesthesia, but before surgery. In the postoperative paracetamol group, patients received IV infusion of paracetamol 1000-2000 mg in the recovery room. Postoperative pain condition was evaluated using the Faces Pain Scale. In the recovery room, an observer recorded the pain score, complaints of nausea and vomiting, the need for rescue analgesics, and the need for antiemetic drug during 24 h postoperatively.

Results: The incidence of nausea and vomiting during the first 24 h postoperatively was significantly lower in the intraoperative paracetamol group than in the postoperative paracetamol group (p=0.05).

Conclusion: The intraoperative administration of paracetamol reduces PONV incidence in morbidly obese patients undergoing laparoscopic bariatric surgery.

Keywords: bariatric surgery, morbid obesity, PONV, multimodal analgesia, paracetamol.

Conflict of interest statement No conflict of interest to disclose.

INTRODUCTION

In the absence of antiemetic prophylaxis, postoperative nausea and vomiting (PONV) occur in 70-80% of patients with morbid obesity (MO) after bariatric interventions. However, the mechanism of the occurrence of PONV in these patients remains poorly understood. PONV frequency is highest after longitudinal resection of the stomach, probably largely mechanical in origin, associated with staple lines and pressure on the stomach tissue [3]. The results of some studies have clearly shown that PONV syndrome is potentially dangerous for different postoperative complications: insufficiency of seams, rupture of esophagus, formation of hematoma, aspiration bronchopneumonitis [7]. PONV is also a major factor in delaying the onset of enteral nutrition and prolonging the length of the patient stay in the hospital. Studies that directly compare the effectiveness of antiemetic drugs after bariatric interventions are not sufficient. The basics of antiemetic practice in bariatry are the same as

those used in general surgery, namely the antagonists of 5-HT₃-ondansetron and dexamethasone. But an important side effect of ondansetron is the prolongation of QT interval and development of TdP (torsades de pointes) – polymorphic ventricular tachycardia. Since patients with MO often have concomitant cardiomyopathy, various types of cardiac arrhythmias, this negative effect of ondansetron can greatly complicate intra- and postoperative periods. In this regard, the maximum daily dose of 32 mg should not be exceeded, as well as with ondansetron should be appointed with concomitant cardiac pathology in patients with MO. [4].

It is known that the main triggers of PONV are opioids and some general inhalation anesthetics. Intravenous administration of paracetamol, as part of the preventive multimodal analgesia, reduces the overall perioperative dose of opioids, but cannot affect the consumption of general anesthetics [5]. However, paracetamol suppresses COX -1, COX -2 enzymes and activates

downward serotonergic inhibitory pathways, and a number of studies suggested that paracetamol can reduce the incidence of PONV [1,2]. We suggested that the inclusion of paracetamol injector in the prevention multimodal analgesia scheme would also be appropriate for the prevention of PONV in patients with MO during laparoscopic bariatric surgery (LBS). Therefore, we investigated the effectiveness of intraoperative versus postoperative injecting paracetamol in patients with morbid obesity in LBS. We also studied the effect of intraoperative and postoperative administration of paracetamol on the use of narcotic analgesics within the first 24 postoperative hours in target groups of patients.

Study objective: to investigate the effect of different modes of intravenous paracetamol as a part of multimodal perioperative analgesia on the incidence of PONV and consumption of opioid analgesics on the first postoperative day in patients with MO after LBS.

MATERIALS AND METHODS

The study included 60 patients with MO: 28 men and 32 women aged from 18 to 61 years, from BMI 37-70 which in the period from 2013 to 2017 underwent LBS in State Scientific Institution "Scientific-Practical Center for Prophylactic and Clinical Medicine". Patients were randomized into 2 groups. The first group (n1 = 30) included patients who intraoperatively (before incision) received 1000 mg paracetamol (Influgan) intravenously as a part of preventive multimodal analgesia. In the second group (n2 = 30) patients intraoperative paracetamol was not used, but patients received 1000-2000 mg of paracetamol (Influgan) per day intravenously as a component of postoperative analgesia. In both groups, patients received premedication with 8 mg of ondansetron intradermally during premedication. The primary efficacy end point – no PONV episodes during the first 24 hours after surgery, and the secondary outcome – no need for additional anesthesia opioid analgesics within 24 hours after surgery.

All patients during the operation had a combined inhaled low-flow anesthesia with sevoflurane in combination with perioperative multimodal analgesia.

Used method of anesthesia – multicomponent balanced anesthesia with the following method: premedication – ondansetron 8 mg, dexketoprofen – 50 mg, pantoprazole – 40 mg intravenously (in the first group (n = 30)). The induction of propofol – 2-2.5 mg / kg fractionally until the clinical symptoms of anesthesia, fentanyl 0.005% – 0.2 mg. Tracheal intubation after relaxation against atracurium benzilate at a dose of 500-600 mg/kg or rocuronium bromid in a dose of 0.6-1.0 mg / kg. Support for anesthesia: oxygen-sevoflurane mixture FiO₂ –

50-55%, sevoflurane – 1.4-1.7 vol.% at exhalation at a flow no more than 1 l/min. BIS parameters were maintained at the level of 40-55. For intraoperative anesthesia, in the first group (n = 30), paracetamol was injected (Influgan, LLC Yuriy-Farm) 1000 mg in the form of intravenous drip-feed at a dose of 2-2.5 mg/kg atm/h. In the second group (n = 32) – fentanyl in a dose of 2.5-3.5 mg / kg atm/h. Relaxation in both groups was supported by the fractional administration of atracurium bezylate in a dose of 10-20 mg every 30-40 minutes or rocuronium bromid in the same dose.

Patient's intraoperative monitoring included: non-invasive measurement of blood pressure, heart rate, pulse oximetry, ECG, central hemodynamics (mathematical method), determination of oxygen concentration, carbon dioxide and inhalation anesthetics on inhalation and exhalation, registration of bispectral index in on-line mode. Intraoperative parameters of acid-base state, electrolytes, blood glucose, venous carbonation were also determined. All patients had catheterization of peripheral veins, and the rate of intraoperative infusion did not exceed 3-5 ml/kg/h.

The level of postoperative pain and PONV was determined on the visual-analytical scale (VAS) [6]. The assessment of pain by VAS was performed for the first time on the operating table, immediately after the tracheal extubation, then at 1, 4, 6, 12 and 24 hours after the operation twice (before and 30 minutes after anesthesia).

Interpreting of VAS scale:

- 0 – no pain;
- 1-3 points – mild pain;
- 4-5 points – moderate pain;
- 6-9 points – severe pain;
- 10 points – the strongest pain.

Interpretation of anesthetizing results:

- 1) no pain – 0 points;
- 2) adequate pain relief – 1-4 points;
- 3) additional pain relief (moderate pain) – 5 points;
- 4) it is necessary to use narcotic analgesics (severe pain) – 6 -10 points.

PONV rate was recorded during the first 24 hours of the postoperative period. The analysis of PONV syndrome was performed on the basis of subjective sensations of patients and the severity of clinical manifestations in case of vomiting. During the study, the number of cases, severity and duration of clinical manifestations of PONV was studied in each group.

A single incident of PONV was considered in patient for one or more of the listed conditions:

- retching
- vomiting
- clinically significant nausea
- independent requirement drugs for nausea.

In order to objectivize the clinical significance of nausea, the scale of the PONV manifestations of the intensity of clinical manifestations, consisting of four points, where 0 – corresponded to the absence of PONV, 1 – manifestation of nausea, 2 – presence of vomiting, 3 – development of repeated vomiting, was used. In the case of two or more episodes of vomiting, ondansetron was administered intravenously at a dose of 4-8 mg [12].

The statistical processing of the study results was carried out using the statistical analysis package EZR (R-Statistics) and the author's package "Medstat" (Lyakh Yu.E., Guryanov VG, 2004-2011).

RESULTS

Dynamics of the level of postoperative pain by VAS in the first day after surgery is presented in Table 1.

Table 1. Parameters of the level of postoperative pain for VAS in the first day after surgery

Postoperative hours	Group of intraoperative paracetamol (n1 = 30)	Median error	Group of postoperative paracetamol (n2 = 30)	Median error
Wakefulness	0.5 (0-3)*	0.191	0 (0-1)*	0.114
2 hours	4 (2-6)*	0.183	5 (4-7)*	0.224
4 hours	4 (3-7)**	0.212	6 (5-8)**	0.200
6 hours	3 (3-5)**	0.130	5 (4-7)**	0.205
8 hours	3 (2-7)*	0.286	4 (3-7)*	0.214
12 hours	3 (2-5)*	0.140	3 (3-5)*	0.130
24 hours	3 (2-4)*	0.136	3 (3-4)*	0.069

* - Comparison of the central tendencies of the two independent populations, the statistically significant differences ($p \geq 0.05$, W Wilcoxon test, multiple comparison, Kruskal-Wallis test, X1 square test) between parameters in the 1 st and 2 nd groups; ** - statistically significant differences ($p \leq 0.05$, T Wilcoxon test, multiple comparison, Kruskal-Wallis test) of the parameters in the comparison groups at 4 and 6 postoperative hours

As can be seen from the presented data, there were no statistically significant differences between the study groups regarding the mean points of pain in the first 24 hours after the operation. In the early postoperative period, the pain level was evaluated using VAS 10-point system. At pain threshold level 2- 5 points by VAS, NSAIDs (dexketoprofen) and paracetamol were used, above 5 points – narcotic analgesics (promedol) [8] were used. Dexketoprofen has a direct and rapid effect on the transduction process, causing a selective blockade of NMDA receptors-the modulation of pain impulse. Paracetamol suppresses COX -2, COX -3 enzymes (perception) and activates downward serotonergic inhibitory pathways in the central nervous system, increased activity of cannabinoid receptors – modulation of pain impulse. Thus, the combination of drugs provides multimodality. The daily dose of dexketoprofen was 100-150 mg, paracetamol – 2000-3000 mg. After the above mentioned

laparoscopic bariatric surgery, the pain level by VAS in patients in the first group did not exceed 4 points on average. Accordingly, there was no need for narcotic analgesics. In patients of the second group, the rates of pain by VAS during the first postoperative period did not significantly differ from the first group of patients, but were significantly increased in the first six postoperative hours. Therefore, patients in this group against NSAIDs (dexketoprofen, paracetamol,) required additional administration of promedol.

As can be seen from Table 2, almost all patients in the second group had manifestations of PONV and required additional postoperative administration of ondansetron, as opposed to those in the first group receiving the first dose of paracetamol intraoperatively. We have found that the incidence of PONV is also related to the level of pain by VAS within the first hours after surgery.

Table 2. Parameters of the PONV occurrence frequency on the first day after surgery

Sample	PONV frequency
group 1 (n1=30)	6,7% (CI = 95 %, 0.6-18.8 , p=0.05)
group 2 (n2=30)	93,8% (CI=95%, 82.4-99.5 p=0.05)

DISCUSSION

Currently, practically insoluble task is an attempt to record and eliminate all factors provoking the development of PONV syndrome in bariatric patients, which explains the high rate of failure in the fight against it [7, 9]. However, modern anesthesiology has achieved some success in preventing this complication of anesthesia. It is believed that the most effective way to solve the problem is to reduce the dose of opioid agonists that have proven powerful emetogenic potential in the perioperative period on alternative systems

of systemic anesthesia [8, 10]. For this purpose, as a substitute for narcotic analgesics in modern literature, it is often recommended to use the drugs of the COX inhibitor group. [11]. For the purpose of pre-emptive analgesia use paracetamol 20 minutes before the operation, the daily dose is 4g. The design of this study made it possible to evaluate the effect of different regimens of paracetamol administration, as a central blocker of COX-2 and COX-3, in the multimodal analgesia scheme on the incidence of PONV inpatients with morbid obesity after laparoscopic bariatric interventions. We have found that the prophylactic administration of paracetamol reduces the frequency of PONV.

Interestingly, the administration time significantly affected the antiemetic effect: the most effective was pre- or intraoperative intravenous administration of paracetamol, but not as a postoperative analgetic.

Despite the preoperative administration of ondansetron, cases of PONV were nevertheless observed in patients of both study groups. But the inclusion of paracetamol in the scheme of preventive multimodal analgesia has greatly reduced the incidence of PONV in patients of the first group. Contrary to our expectations, the decrease of PONV was not associated with a reduction of the total dose of morphine equivalents; however, this was associated with decreased pain intensity. Among clinicians are believed that pain itself can be a risk factor for PONV. Another potential mechanism is the direct antiemetic effect of paracetamol. In fact, paracetamol is metabolized in the brain in the AM404 metabolite, which is capable of inhibiting of reuptake of anandamide, known as the cannabinoid CB1 and CB2 receptors agonist. It was shown that decreased level of anandamide is associated with increased frequency of nausea and vomiting in humans [13]. Therefore, we believe that paracetamol has a direct effect on the frequency of PONV increasing the level of anandamide. The results of this work confirm the presence of paracetamol in its own antifertile effect in patients with morbid obesity.

In connection with obtained data, an application for a utility model was submitted.

CONCLUSIONS

1. Paracetamol reduces the frequency of PONV provided pre- or intraoperative administration, but not with post-operative anesthesia.
2. The inclusion of paracetamol in the scheme of preventive multimodal analgesia in patients with MO during LBS avoids the need for the use of narcotic analgesics in the scheme of postoperative anesthesia.

3. The anti-emetic effects of intravenous intraoperative administration of paracetamol are related not only to the reduction of the total dose of opioids, but also to the direct mechanisms of the effect of paracetamol on the emetogenic centers of the central nervous system.
4. Pain is an independent factor of PONV along with well-known triggers – opiates and hypnotics.

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ВЛИЯНИЕ ИНТРАОПЕРАЦИОННОГО ВНУТРИВЕННОГО ВВЕДЕНИЯ ПАРАЦЕТАМОЛА В СРАВНЕНИИ С ПОСТОПЕРАЦИОННЫМ НА ЧАСТОТУ ПОСЛЕОПЕРАЦИОННЫХ ТОШНОТЫ И РВОТЫ У ПАЦИЕНТОВ С МОРБИДНЫМ ОЖИРЕНИЕМ ПОСЛЕ ЛАПАРОСКОПИЧЕСКИХ БАРИАТРИЧЕСКИХ ВМЕШАТЕЛЬСТВ

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Резюме

Целью данного исследования явилось сравнение эффективности интра- и постоперационного введения парацетамола на частоту возникновения ПОТР у пациентов с морбидным ожирением после лапароскопических бариатрических вмешательств.

Материалы и методы. В исследовании приняли участие 60 пациентов, рандомизированные на 2 группы (n=30). В первой группе пациенты получали внутривенную инфузию парацетамола в дозе 1000 мг во время анестезии, но до хирургического разреза. Во второй группе пациенты получали внутривенную инфузию парацетамола 1000-2000 мг в качестве постоперационного обезболивания в первые 24 ч. Уровень послеоперационной боли оценивали с использованием визуально-аналоговой шкалы. Была проведена оценка боли, жалоб на тошноту и рвоту, потребность в дополнительном введении наркотических анальгетиков и потребность в противорвотных средствах в течение 24 часов после операции.

Результаты. Частота тошноты и рвоты в течение первых 24 ч после операции была значительно ниже в первой группе пациентов, в сравнении с группой постоперационного введения парацетамола (p = 0,05).

Ключевые слова: бариатрическая хирургия, морбидное ожирение, ПОТР, мультимодальная анальгезия, парацетамол

ЧЕРНИЙ В.І., ЄВСЄЄВА В.В.

ВПЛИВ ІНТРАОПЕРАЦІЙНОГО ВНУТРІШНЬОВЕННОГО ВВЕДЕННЯ ПАРАЦЕТАМОЛУ В ПОРІВНЯННІ З ПОСТОПЕРАЦІЙНИМ НА ЧАСТОТУ ПІСЛЯОПЕРАЦІЙНИХ НУДОТИ ТА БЛЮВАННЯ У ПАЦІЄНТІВ З МОРБІДНИМ ОЖИРІННЯМ ПІСЛЯ ЛАПАРОСКОПІЧНИХ БАРИАТРИЧНИХ ВТРУЧАНЬ

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Резюме

Метою даного дослідження є порівняння ефективності інтра- та пост-операційного введення парацетамолу на частоту виникнення ПОНБ у пацієнтів з морбідним ожирінням після лапароскопічних бариатричних втручань.

Матеріали та методи. В дослідженні взяли участь 60 пацієнтів, поділені на 2 групи (n = 30). У першій групі пацієнти отримували внутрішньовенну інфузію парацетамолу в дозі 1000 мг під час анестезії, але до хірургічного розтину. В другій групі пацієнти отримували внутрішньовенну інфузію парацетамолу 1000-2000 мг в якості післяопераційного знеболення в перші 24 післяопераційні години. Рівень післяопераційного болю оцінювали за допомогою візуально-аналогової шкали. Було проведено оцінку болю, жалоб на нудоту та блювання, потреба в допоміжних анальгетиках і потреба в протиблювотних засобах протягом 24 годин після операції.

Результати. Частота нудоти та блювання протягом перших 24 годин після операції була значно нижчою в першій групі пацієнтів, у порівнянні з групою пост-операційного введення парацетамолу (p = 0,05).

Ключові слова: бариатрична хірургія, морбідне ожиріння, ПОТР, мультимодальна анальгезія, парацетамол.