



V. P. Andryushchenko, V. V. Kuhn, D. V. Andryushchenko
Danylo Galitsky Lviv National Medical University

MULTIMODAL ANALGESIA AS AN EFFECTIVE COMPONENT IN TREATMENT PROGRAM FOR ACUTE PANCREATITIS

The aim — to study the multimodal analgesia clinical efficacy in complex surgical treatment of patients with acute pancreatitis.

Materials and methods. The treatment results of 48 patients with acute pancreatitis who were treated at the city pancreatologic center in General surgery clinic have been analysed. Patients were aged from 46 to 58 years (mean age — 54.3 ± 5.2) years). Eleven (23 %) women and thirty-seven (77 %) men took part in the research. Patients were randomly divided into two groups: in the main group ($n = 25$) the treatment program, in addition to basic infusion therapy, a multimodal analgesia was provided; in the comparison group ($n = 23$) anesthesia was performed by analgesic non-opioid drugs appointment. Multimodal analgesia included coapplication of analgesics, *Infulgan* antipyretics (10 mg paracetamol contains in 1 ml) and NSAID *Diclobru* (diclofenacum).

Results and discussion. In the study group, in contrast to the comparison group a significant tendency to a pain decreased by its visual analog scale assessment and in the cortisol serum level was shown. The absence of significant positive analgesia result suggested the severe acute pancreatitis presence.

Conclusions. The proposed multimodal anesthesia method should be used in clinical practice due to its effectiveness and the modern FastTrask surgery principle relevance.

Key words: multimodal analgesia, acute pancreatitis, *Infulgan*.

Acute pancreatitis (AP) is one of the most serious, prognostically unfavourable and often threatening acute diseases of the abdominal cavity. The problem of treatment of patients with AP is a socio-medical [1, 2, 10]. This is due to the fact that the number of patients with this disease is increasing with a predominance of males of working age, and treatment, particularly surgical, is associated with long term hospitalization, considerable costs, high frequency of adverse events, often - resulting in a disability [5, 7, 9, 13]. Widely recognized approach is based on the comprehensive therapy with a combination of operational and non-interventional therapeutic techniques namely with domination of multidisciplinary principle [6, 8, 11, 14]. Reduction or alleviation of pain syndrome (PS) is essential in medical treatment of AP and

its complications [2, 7, 9, 12]. This is due to the fact that the significant PS inherent in AP not only adversely affects the patient's subjective esthesia, but also is an important part of pathogenetic mechanisms of development and progression of the disease [2, 4, 6, 8, 15]. Therefore, the development of new approaches to the alleviation of PS by combining medications of different pharmacodynamic effects according to the principle of multimodal pain control is of scientific and practical interest.

The aim of research is to study the clinical effectiveness of multimodal analgesia in comprehensive surgical treatment of patients with acute pancreatitis.

MATERIALS AND METHODS

The results of treatment of 48 patients with AP, who were receiving medical treatment

at the specialized city centre of pancreatology based on the clinic of general surgery of Danylo Galytsky Lviv National Medical University has been analysed. The patients' age - from 46 to 58 years (mean age - 54.3 ± 5.2 years). There were 11 (23 %) women and 37 (77 %) men.

Diagnosis of the disease was made according to the results of the clinical, laboratory-biochemical, radiological (ultrasonography, computerised tomography, roentgenography) and instrumental (fibrogastroduodenoscopy, videolaparoscopy) methods of study. Duration of the disease on admission ranged from 2 to 4 days, in most patients (35; 73%) - 2 days. Rapid progression of the disease was detected in 17 (35%) cases.

AP of ethanol genesis was found in 35 (73%) patients, of biliary one - in 13 (27%). According to the classification (Atlanta, 2012) [6], the mild course of the disease was ascertained in 26 (54%) patients, moderate - in 15 (31%) and severe - in 7 (15%) patients.

All patients were divided into two groups in random manner. 25 patients whose medical program, in addition to basic medication infusion therapy, included multimodal analgesia by intravenous administration of medicinal product from the group of analgesics-antipyretics - "Infulgan" (paracetamol) in combination with NSAIDs "Diclobru" (diclofenac), has been enrolled in the main group. Comparison group included 23 patients, whose pain control was provided by the prescription of non-opioid analgesics.

Elaborated method of multimodal analgesia provided for the use of "Infulgan" (paracetamol 1000 mg/100 ml) in combination with the "Diclobru" (diclofenac sodium 3.0 ml/75 mg) according to the scheme: during the first hours after hospitalization, intravenous "Infulgan" was administered in a dose of 100 ml (1000 mg) three times daily (4 hours apart) with a single intramuscular prescription of "Diclobru" in a dose of 3.0 ml (75 mg). The "Infulgan" has been selected as a component of a multimodal analgesia, since according to the recommendations of the European Association of Regional Anaesthesia (ESRA) paracetamol, which is the main active ingredient of the drug - an integral component of mild, moderate and severe PS reduction [5, 13]. On the second day of treatment, dose of "Infulgan" was reduced (1000 mg/100 ml 2 times daily intravenously).

A comprehensive intensive conservative infusion-medical therapy had a positive effect in 22 (88%) patients of the main group and 18 (78%) - of comparison group, and led to dissipation of pancreatic infiltrate with its abortive development.

Due to the progression of AP and development of local purulent necrotic complications, such as parapancreatitis/paracolitis,

surgery was performed in 3 (12%) patients of the main group and 5 (22%) - of the comparison group, using minimally invasive (intervention sonography and videolaparoscopy), conventional laparotomic surgical technology, and combinations thereof. The scope of open surgeries involved a thorough revision of the pancreas and parapancreatic spatiums to identify all necrotic zones ("necrotic roads") and their debridement. Expansion of purulent necrotic process has been identified in mesenteric-mesocolitic (64% of cases), paracolic (21%), paranephric (7%) and subdiaphragmatic (6%) areas. A necrosectomy with the formation of laparoretroperitoneotomy as a prerequisite for further debridements by programmable relaparotomies.

Assessment of pain intensity carried out on the basis of its subjective perception by patient using a visual analogue scale (VAS) [15]. 20-point linear scale on which the digital indicator of the pain intensity (4 points was given to each gradation) associated with a certain colour was used: no pain (white), mild pain (green), moderate (yellow), severe (brown) unbearable (red).

The level of hormone cortisol (stress hormone) in the blood measured by electrochemiluminescent method in a certified laboratory "Medis" was used as biochemical criteria of alleviation of PS. The study was conducted on admission, on the second, fourth and seventh day of treatment. A study was conducted in the morning in the fasted state, since the peculiarity of cortisol in the blood is a variation of its concentration throughout the day. 171.0 - 536.0 nM/L was taken as normal hormone level in the morning according to laboratory "Medis".

The results have been processed by methods of variation statistics using Student-Fischer test.

RESULTS AND DISCUSSION

The use of multimodal analgesia techniques contributed to alleviation of PS during the first 3 hours of treatment in 21 (84%) of 25 patients of the main group (tab. 1).

Dynamics of alleviation of PS in patients of the main group was more significant (see Table 1). Thus, the credible reduction of PS intensity, tending to its complete alleviation after 3 hours, has been detected starting from 30 minutes after administration of drugs. Credible reduction of PS intensity has been ascertained in the comparison group only after an hour, and its complete alleviation - the third hour of observation. Thus, the use of proposed method contributed to pain control effect on the first day in 21 (84%) patients of the main group and in 17 (73.9%) - of the comparison group.

Table 1
Dynamics of pain intensity according to
a visual analogue scale, scores

Parameter	Main group (n = 25)	Comparison group (n = 23)
On admission	19 ± 1	18 ± 2
After 15 minutes of therapy	14 ± 2	16 ± 2
After 30 minutes of therapy	11 ± 1*	14 ± 2
After 45 minutes of therapy	9 ± 1*	13 ± 2
After 1 hour of therapy	8 ± 1*	10 ± 1*
After 3 hours of therapy	6 ± 2*	8 ± 3*

* The difference in the value on admission is statistically significant ($p < 0.05$).

Table 2
Dynamics of pain intensity depending on the severity of
acute pancreatitis, scores

Parameter	Mild (n = 26)	Moderate severity (n = 15)	Severe (n = 7)
On admission	12 ± 1	17 ± 1	19 ± 2
After 1 hour of therapy	7 ± 1*	13 ± 1.6	14 ± 2
After 3 hours of therapy	5 ± 1*	9 ± 2*	13 ± 1

* The difference in the value on admission is statistically significant ($p < 0.05$).

Table 3
Cortisol level dynamics in the blood, nmol/l

Day	Main group (n = 25)	Comparison group (n = 23)
1st	1041 ± 12	997 ± 18
2nd	685 ± 24*	786 ± 21
4th	453 ± 21*	569 ± 19
7th	342 ± 14*	487 ± 17*

* The difference in the value on admission is statistically significant ($p < 0.05$).

Analysis of clinical efficacy of multimodal analgesia in patients with varying severity of AP (tab. 2) showed credible reduction of the intensity of PS after 1 hour treatment with its complete alleviation during the third hour in case of in mild clinical course of the disease

per hour. Statistically significant reduction of PS has been ascertained only after 3 hours in case of moderate AP. PS was not reversed in patients with severe AP after 3 h, which required an additional use of opium analgesics or peridural anesthesia. The dynamic of intensity reduction of PS, using the proposed method of analgesia, reflected the severity of the clinical course of the disease, which can be used as one of the criteria for assessment of the severity and prognosis of AP.

The analysis of blood cortisol level dynamics (Table 3) showed tendency to cortisol reduction at high primary parameter in the main group, since the second day, and its normalization - the seventh day, while there was credible reduction of the concentration of said hormone in the comparison group only on the fourth day.

Thus, the use of multimodal analgesia according to elaborated scheme has contributed to the alleviation of PS in patients with AP according to clinical data and the level of stress hormone cortisol in the blood. The lack of reliable reduction of PS dynamics can be considered as an indirect criterion of severe and prognostically adverse course of the disease.

The principle of multimodal analgesia proposed by H. Kehlet [4], the essence of which is the concomitant use of drugs of different pharmacological action, contributing to amplification of pain relief, has opened new opportunities in dealing with the alleviation of PS in clinical medicine, particularly in the abdominal surgery [5, 11 14]. According to the FastTrak principle [13], which is widespread in Europe, opioids are not applicable to relieve PS in pre- and postoperative periods.

Combination of two drugs - "Infulgan" and "Diclobru" had a positive effect based on their synergistic action, which gives reason to recommend them for use in clinical practice.

CONCLUSIONS

Multimodal analgesia, which provides for concomitant use of "Infulgan" and NSAIDs - is effective and pathogenetically grounded component of comprehensive surgical treatment of patients with acute pancreatitis.

The degree of pain intensity and dynamics of its reduction using the proposed method of analgesia may be an indirect criterion for assessment of the severity and prognosis of acute pancreatitis.

References

1. Дронов О. І., Ковальська І. О. Гострий панкреатит: визначення, принципи діагностики та лікування // Здоров'я України. — 2010. — С. 28 — 29.
2. Овечкин А. М. Профилактика послеоперационного болевого синдрома. Патогенетические основы и клиническое применение: Автореф. дис. ...д-ра мед. наук. — М., 2000. — 42 с.
3. Патент на корисну модель № 43219 А 61В 10/00 Україна. Спосіб визначення ступеня болю у хворих із травмою грудної клітки та живота у ранньому періоді захворювання за допомогою візуально-аналогової шкали / Куновський В. В., Матвійчук Б. О., Квіт А. Д., Магльований В. А. — № u200901908. — Заявка від 03.03.2009.; Опубл. 10.08.09. — Бюл. № 15, 2009.
4. Патент на корисну модель № 44812 А 61К 31/135 Україна. Спосіб до-та післяопераційного знеболювання хворих з гострим панкреатитом / Куновський В. В., Андрущенко В. П., Андрущенко Д. В., Фусс Ю. О. — № u 2009 05773. — Заяв. 05.06.2009.; Опубл. 12.10.09. — Бюл. № 19, 2009.
5. Acute Pain Management: Scientific Evidence. Australian and New Zealand College of Anaesthetists, 2nd ed. (endorsed Royal College of Anaesthetists, UK), 2005.
6. Bakker O. J., van Santvoort H., Besselink M. G. et al. Extrapancratic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? // Gut. — 2012. — Vol. 18. — P. 143 — 149.
7. Banks P. A., Bollen T. L., Dervenis C. et al. Classification of acute pancreatitis — 2012: Prevision of Atlanta classification and definitions by international consensus // Gut. — 2013. — Vol. 62. — P. 102 — 111.
8. Gardner T. B., Vege S. S., Pearson R. K. et al. Fluid resuscitation in acute pancreatitis // Clin. Gastroenterol Hepatol. — 2008. — N 6. — P. 1070 — 1076.
9. Kehlet H., Holte K. Effect of postoperative analgesia on surgical outcome // Br. J. Anaesth. — 2001. — Vol. 87. — P. 62 — 72.
10. Marion B. M., Van der Kolk, Graham Ramsaj. Management of acute pancreatitis in the intensive care units // Current option in Critical Care. — 2000. — N 6. — P. 271 — 275.
11. Mofidi R., Duff M. D., Wigmore S. J. et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis // Br. J. Surg. — 2006. — Vol. 93. — P. 738 — 744.
12. Papachristou G. I., Muddana V., Yadav D. et al. Increased serum creatinine is associated with pancreatic necrosis in acute pancreatitis // Am. J. Gastroenterol. — 2010. — Vol. 105. — P. 1451 — 1452.
13. Postoperative Pain Management — Good Clinical Practice. General recommendations and principles for successful pain management. Produced with the consultations with the Europeans Society of Regional Anaesthesia and Pain Therapy. Project chairman N. Rawal, 2005. — 57 p.
14. Wall I., Badalov N., Baradaran R. et al. Decreased morbidity and mortality in patients with acute pancreatitis related to aggressive intravenous hydration // Pancreas. — 2011. — Vol. 40. — P. 547 — 550.
15. Zoua P., Stigler J., Maly T. Do we really apply fast track surgery // Britsl. Lek Listy. — 2008. — Vol. 109, N 2. — P. 61 — 65.