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## EFFICACY AND SAFETY OF INFULGAN ADMINISTRATION IN PERIOPERATIVE ANALGESIA IN INJURED PERSONS HAVING THE TRAUMATIC DISEASE IN THE CLINICAL PRESENTATION OF POLYTRAUMA

**Summary.** The paper deals with the efficacy and safety of applying a comprehensive context-dependent approach using Infulgan in perioperative pain management in injured persons with posttraumatic pain syndrome in clinical presentation of polytrauma in terms of the concept of comorbidity.

**Key words:** comorbidity, polytrauma, pain syndrome, paracetamol, perioperative pain management.

### Introduction

#### Concept of comorbidity

**Comorbidity** is a coexistence of two and/or more syndromes (transsyndromal comorbidity) or conditions (transnosological comorbidity) in one patient, which are pathogenically interrelated or simultaneous (chronological comorbidity) [1].

In the structure of comorbidity, one can distinguish:

- causal comorbidity, which is caused by a concurrent damage to various organs and systems due to one pathologic agent;
- complicated comorbidity, which results from the underlying disease and, generally, in a while after its destabilization, subsequently manifests in the form of target lesions;
- iatrogenic comorbidity, which manifests in case of necessary physician's negative impact on the patient providing that the danger of any given medical procedure has been preestablished;
- unspecified comorbidity, which assumes the presence of singular pathogenetic mechanisms of development of diseases comprising this combination, but requires a number of tests proving the hypothesis of the researcher or physician;
- «coincidental» comorbidity, which refers to initial algism of the combination of diseases.

When formulating a clinical diagnosis of a comorbid patient, following diseases are distinguished: primary disease; concurrent diseases; coexistent diseases; underlying disease: complications and concomitant diseases.

Table 1 shows the main comorbid pathology observed in surgical patients (Izhevsk, Russia).

The number of comorbid conditions significantly increases with age. Comorbidity rate increases from 10 % at the age under 19 up to 80 % in persons aged 80 and older [2, 3].

Comorbidity is widely represented among patients hospitalized at multidisciplinary hospitals. The simultaneous presence of several diseases in the clinical presentation of emergencies in patients of an emergency hospital is the rule rather than the exception [4, 5].

Many years of experience of the Polytrauma Department of the Kharkiv City Clinical Emergency and Immediate Care Hospital named after Professor O. I. Meshchaninov confirms that the concept of comorbidity determines the severity of the traumatic disease in virtually 100% of clinical situations.

These theses are clearly illustrated by the structure of mortality at Anaesthesia and Intensive Care Units (AICUs) at multidisciplinary hospitals and AICUs of Polytrauma for 2011 that is presented in Fig. 1.

The overall mortality rate in the clinical presentation of polytrauma was higher by 3.69 % and the mortality rate in the first 24h after hospitalization exceeded these indices by 33.64 % at the AICU of the Multidisciplinary Clinical Hospital, which reflects the primary severity in injured persons with multisystem injuries. In the structure of age-related mortality at the AICU of Polytrauma, injured working-age persons predominate (more than by 20 %), while the number of senior or elderly persons is by 22.33 % less than at the AICU of the Multidisciplinary Clinical Hospitals, which reflects the structure of injured persons with polytrauma where young and middle-aged persons significantly predominate.

**Table 1. Prevalence of comorbid conditions of the main organs and systems in case of surgical pathology**

| Comorbid Conditions          | Prevalence rate |
|------------------------------|-----------------|
| Respiratory System           | 20.3            |
| Digestive System             | 38.6            |
| Urinary System               | 17              |
| Endocrine System             | 30.7            |
| Locomotor System             | 19.6            |
| Arterial Hypertension        | 35.2            |
| Chronic Alcoholism           | 9.2             |
| Chronic Venous Insufficiency | 9.8             |
| Anomie (Iron Deficiency)     | 3.5             |

## Polytrauma

By polytrauma, we mean severe multiple organ and multisystem injuries, in which the traumatic disease occurs. Its features are: the development of mutual burden syndrome, atypical symptoms of injuries, the complexity of diagnosis, the necessity of a continuous assessment of the patient condition severity, an unstable compensation of a condition and the urgent need for an adequate therapeutic intervention at specialized centers, as well as a great number of complications and a high mortality rate.

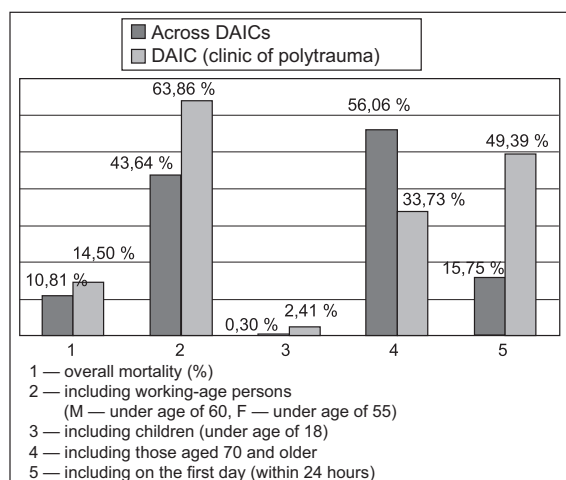
In case of damaging effects, all mechanisms of body responsiveness activate. First, the adaptive behavioural responses of preventing or fighting the corresponding vegetative components are urgently triggered. Then, compensatory reactions start followed by the general adaptation syndrome. However, in case of severe, life-threatening influence, these reactions turn out to be unviable. Moreover, as a result of an abrupt, wasteful and unjustified consumption of functional and energy resources in inflammatory catabolism, they reduce the probability of survival [6, 7].

## Pain syndrome — an etiopathogenetic component of the traumatic disease

Based on the submitted data, it should be indicated that a traumatic injury is a causal etiological factor in the development of the traumatic disease; it just is the releaser of nociception determining the pain syndrome development. So, it becomes clear how important the pain syndrome is in the course of the traumatic disease — from the very beginning, it takes on the significance of one of its main etiopathogenetic components.

From the very beginning of its onset, the posttraumatic pain syndrome (PTPS) is acute, nociceptive (somatogenic), and multimodal (comprising, to various extents, somatic, visceral, and neurogenic components).

Life-threatening extremal impact leads to impairment of the damaged organ functions and biological sustainability of the body. At that, the pain input rapidly changes from the initial danger warning into a kind of “noise” that masks out or distorts regulatory signaling non-nociceptive emergency input. Therefore, the pain weakens the necessary and enhances the pathological components of the extremal response, and renders the pathological process course more severe. Hence, struggling with the pain syndrome is quite natural.



**Figure 1. Overall mortality rates at DAICs of multidisciplinary hospitals and the DAIC of the Clinic of Polytrauma**

## Conceptual prerequisites for the development of the pain syndrome treatment regimens in the clinical presentation of polytrauma

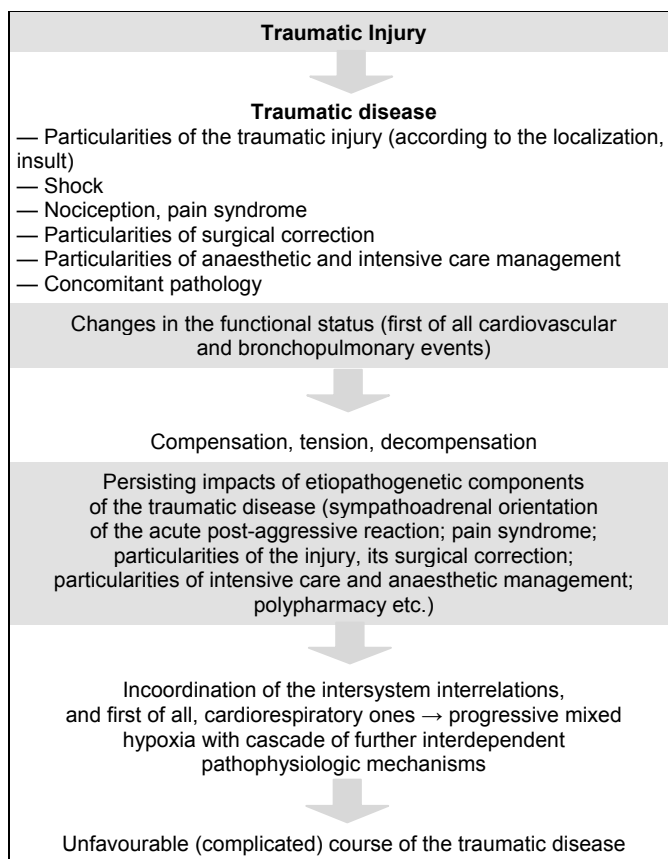
The presence of comorbidity, the necessity to influence all the etiopathogenetic components of the traumatic disease lead to natural polypharmacy. Polypharmacy, especially in elderly and senile patients, contributes to a sharp rise in the possibility of local and systemic adverse effects of drug therapy.

The simultaneous prescription of multiple drugs requires a strict control of the drug compatibility and a thorough compliance with the rules of the rational pharmacotherapy, one of which is the postulate of E. M. Tareev: “Every medicine that is not indicated is contraindicated”.

Among the most important directions of the pain syndrome management, the following should be emphasized:

- 1) preemptive analgesia;
- 2) balanced analgesia;
- 3) patient-controlled analgesia.

Balanced analgesia inherently involves the prevention of plastic changes in neuronal activity of the nociceptive CNS structures due to the total blockade or maximum limitation of the perioperative nociceptive input. This determines the multimodal approach in the use of analgesics with different points of influence taking into account their synergic or cumulative effect. Pain management controlled by the patient allows the most flexible varying the analgesic dose depending on the real needs of the patient. Multimodality of the pain syndrome pharmacotherapy is assured by using of different groups of medications that have an effect on different links of the nociceptive system for these purposes.



**Figure 2. Algorithm of the development of the traumatic disease complicated course (A. A. Khizhniak, A. V. Beletskiy, 2004)**

**Table 2. General characteristics of the study group**

| Characteristics                                                                | Index<br>(n = 98) |
|--------------------------------------------------------------------------------|-------------------|
| Gender (absolute data), m/f                                                    | 62/36             |
| Age (years)                                                                    | 20-72             |
| Combination of injuries — number of injured AFR from 1 to 5 ( $M \pm \sigma$ ) | $2.8 \pm 0.8$     |
| Skin/soft tissues (absolute data)                                              | 97                |
| Head/neck (absolute data)                                                      | 59                |
| Chest (absolute data)                                                          | 23                |
| Abdomen (absolute data)                                                        | 43                |
| Extremities (absolute data)                                                    | 55                |
| ISS, score ( $M \pm \sigma$ )                                                  | $20.0 \pm 4.2$    |

**Table 3. Combination of AFR injuries in the study group (n = 98)**

| Combination of injuries                                       | Abs. |
|---------------------------------------------------------------|------|
| Skin/soft tissues + head/neck + chest + abdomen + extremities | 8    |
| Skin/soft tissues + head/neck + chest + abdomen               | 1    |
| Skin/soft tissues + head/neck + chest + extremities           | 1    |
| Skin/soft tissues + head/neck + abdomen + extremities         | 2    |
| Skin/soft tissues + head/neck + chest                         | 4    |
| Skin/soft tissues + head/neck + abdomen                       | 13   |
| Skin/soft tissues + head/neck + extremities                   | 28   |
| Skin/soft tissues + chest + abdomen                           | 6    |
| Skin/soft tissues + chest + extremities                       | 3    |
| Skin/soft tissues + abdomen + extremities                     | 2    |
| Skin/soft tissues + chest                                     | 5    |
| Skin/soft tissues + abdomen                                   | 12   |
| Skin/soft tissues + extremities                               | 13   |

Among the drugs that are advisable to be included into combined analgesic regimens in patients with the traumatic disease the following ones should be named: local anaesthetics, nonsteroidal anti-inflammatory drugs, narcotic analgesics, ketamine in subnarcotic doses, anticonvulsants.

The conventional practice of using opiates and opioids with existing technologies is certainly effective; however, it is fraught with adverse effects, such as respiratory depression, suppression of gastrointestinal tract, bile duct and bladder motility. Nonsteroidal anti-inflammatory drugs have the ulcerogenic potential, and even in therapeutic doses may have oto-, nephro-, and hepatotoxicity. The use of anticonvulsants, local anaesthetics also has a number of limitations and the possibility of adverse effects [8–11].

In this regard, paracetamol, which has been used in the clinical setting since 1894, is of interest. The drug rapidly passes through the blood-brain barrier, selectively inhibits prostaglandin synthesis in the CNS. Paracetamol does not produce the sedative effect, does not cause nausea, vomiting, and respiratory depression, does not influence on such important indices as platelet aggregation and clotting time, and does not have ulcerogenic effect. The emergence of paracetamol in a form for parenteral administration has significantly expanded the indications and possibilities of its use

in clinical practice. This form is presented in Ukraine by Infulgan manufactured by YURiA-PHARM, LLC. Infulgan is released in the form of solution for infusion containing paracetamol 10 mg/1 ml in 20, 50 and 100 ml vials. The recommended maximum single dose is 1,000 mg; the maximum daily dose is 4,000 mg; the interval between the drug administrations should be NLT 4 hours. The contraindications for Infulgan use are hypersensitivity to paracetamol and other components of the drug, severe hepatocellular insufficiency. In paediatric practice, the drug is used in 1-year old children and older having the body weight > 10 kg [12–14].

The objective of the study was developing optimal variants of perioperative and posttraumatic analgesia (PTPS — posttraumatic pain syndrome) in injured persons with the traumatic disease; the study of efficacy and safety of Infulgan administration in perioperative analgesia in injured persons with PTPS in clinical presentation of polytrauma with due regard to the concept of comorbidity.

## Materials and methods of the study

Since 2012, at the Anaesthesiology and Intensive Care Unit for persons with concomitant injuries, we had begun using parenteral paracetamol — Infulgan manufactured by YURiA-PHARM, LLC — with the purpose of perioperative and posttraumatic analgesia (PTPS) in patients with the traumatic disease. The study group included injured persons with the traumatic disease in the clinical presentation of polytrauma — total number of 98 patients: 62 men and 36 women aged 20 to 72. The general characteristics of the study group, as well as combinations of AFR (anatomical and functional regions) injuries in the study group are shown in Tables 2 and 3.

Moreover, during the perioperative examination, the following concomitant diseases were diagnosed in the study group:

- Coronary artery disease — 28 patients (25.5%);
- Chronic obstructive pulmonary disease (COPD) — 28 patients (28.5 %);
- Chronic gastritis, gastroduodenitis — 32 patients (32.6%);
- Ulcer disease — 9 patients (9.1 %);
- Chronic cholecystitis — 5 patients (5.1 %);
- Chronic pancreatitis — 6 patients (6.1 %);
- Chronic pyelonephritis — 8 patients (8.1 %);
- Obesity — 12 patients (12.2 %);
- Diabetes mellitus — 11 patients (11.2 %).

The clinical evaluation of pain was performed using the visual analogue scale; the quality of the antinociceptive protection was simultaneously evaluated.

All patients received premedication that included, depending on the clinical situation, atropine at a dose of  $0.075 \pm 0.005$  mg/kg, morphine hydrochloride at a dose of  $0.13 \pm 0.02$  mg/kg, relanium at a dose of  $0.12 \pm 0.02$  mg/kg. When performing therapeutic and diagnostic surgical procedures (pleural punctures, laparocentesis), anaesthesia was supplemented with local anaesthesia (0.5% novocaine 10-30 ml). If subsequent surgical correction was needed, the method of anaesthesia was chosen depending on the patient's condition, diagnostic findings, and the extent of the further surgical intervention. All patients were intraoperatively administered Infulgan 1000 mg (100 ml) by IV drip infusion.

After the end of the surgical stage and the transfer to the ICU, the injured persons received Infulgan as the antinociceptive protection at a dose of 1,000 mg 3 to 4 times daily.

Taking into account the similar efficacy of paracetamol doses equivalent to conventionally used NSAIDs, the latter were not applied. Antinociceptive therapy was supplemented, if necessary, by administration of opiates, antihistaminics and sedatives. With the stabilization of the central hemodynamics and the absence of absolute contraindications to the use of local anaesthetics, the pain syndrome management was supplemented by prolonged afferent blockades — conventional or minimally invasive.

### Results of the authors' studies

All the injured persons, on admission, had a shock period of the traumatic disease; at that, 33 of them were diagnosed with decompensated traumatic shock with the pronounced haemorrhagic component.

The sensations of pain on admission to the clinic were evaluated by the injured persons as severe and very severe (Table. 4).

**Table 4. Clinical evaluation of pain on admission (standard units)**

| Clinical evaluation of pain | Mean value (M ± σ) |
|-----------------------------|--------------------|
| VAS-1 (standard units)      | 68.2 ± 7.5         |
| VAS-2 (standard units)      | 87.5 ± 4.5         |

After the end of the surgical stage and the transfer to the ICU, the patients received intensive therapy complex with due regard for the severity of their condition and existing concomitant pathology. The pain syndrome management was performed according the regimen suggested above with the use of parenteral paracetamol. With the completion of postoperative analgesia and recovery of consciousness, all patients assessed the quality of perioperative analgesia as "satisfactory" and "good". In 38 injured persons, the need for prescribing opiates was limited by the first 24 hours of the perioperative period; in 12 — by two days; and 48 patients did not need prescribing them.

In all patients of the study group, we managed to avoid the development of pronounced multiple organ failure; the presence of a concomitant pathology did not result in a critical deterioration in the condition. In none of the clinical situations, complications related to perioperative analgesia were observed.

### Conclusions

1. The suggested regimen of perioperative analgesia with the use of Infalgan may be successfully applied in combination therapy of the traumatic disease.

2. In most cases, the use of Infalgan allows avoiding polypharmacy and, as a result, the adverse effect due to the administration of certain drugs.

3. Including paracetamol in the regimen of perioperative analgesia with due regard for comorbidity is advisable and safe.

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