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Postoperative pain management in non-traumatic emergency general surgery: WSES-GAIS-SIAARTI-AAST guidelines

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BACKGROUND. Timeous emergency surgical treatment should be supplemented with high-quality perioperative care, performed by multidisciplinary teams trained to identify and handle complex postoperative courses. Uncontrolled or poorly controlled acute postoperative pain may result in significant complications. While pain management after elective surgery has been standardized in perioperative pathways, the traditional perioperative treatment of patients undergoing emergency surgery is often a haphazard practice. The present recommended pain management guidelines are for pain management after non-traumatic emergency surgical intervention.

MATERIALS AND METHODS. An international expert panel discussed these issues in subsequent rounds. Four international recognized scientific societies: World Society of Emergency Surgery (WSES), Global Alliance for Infection in Surgery (GAIS), Italian Society of Anesthesia, Analgesia, Intensive Care (SIAARTI), and American Association for the Surgery of Trauma (AAST), endorsed the project and approved the final manuscript.

CONCLUSIONS. Dealing with acute postoperative pain in the emergency abdominal surgery setting is complex, requires special attention, and should be multidisciplinary. Analgesic approach to the various situations and conditions should be patient based and tailored according to procedure, pathology, age, response, and available expertise. A better understanding of the pathomechanisms of postoperative pain is necessary to improve prophylactic and treatment strategies.

KEY WORDS: pain management, postoperative pain, emergency surgery.

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Лікування післяопераційного болю в нетравматичній невідкладній загальній хірургії: рекомендації WSES-GAIS-SIAARTI-AAST

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ОБҐРУНТУВАННЯ. Своєчасне невідкладне хірургічне лікування має доповнюватися високоякісним післяопераційним доглядом, який забезпечують мультидисциплінарні команди, навчені виявляти складні післяопераційні випадки та вести таких пацієнтів. Неконтрольований або погано контрольований гострий післяопераційний біль може призвести до значних ускладнень. Тоді як періопераційне лікування болю при планових операціях є стандартизованим, періопераційне лікування в разі невідкладних операцій часто проводиться на розсуд лікаря. Ці рекомендації стосуються лікування болю після нетравматичного невідкладного хірургічного втручання.
МАТЕРІАЛИ ТА МЕТОДИ. Міжнародна група експертів у кілька етапів обговорювала ці питання. Чотири міжнародно визнані наукові товариства (Всесвітнє товариство невідкладної хірургії – WSES; Глобальний альянс з інфекцій у хірургії – GAIS; Італійське товариство анестезії, знеболення й інтенсивної терапії – SIAARTI; Американська асоціація травматологічної хірургії – AAST) схвалили цей проєкт і затвердили остаточний текст.
ВИСНОВКИ. Лікування гострого післяопераційного болю в умовах невідкладної абдомінальної хірургії є складним, потребує особливої уваги та має бути мультидисциплінарним. Підхід до аналгезії при різних ситуаціях і станах має бути індивідуалізованим й адаптованим до процедури, патології, віку, відповіді пацієнта та наявного в лікаря досвіду. Для вдосконалення профілактичних і лікувальних стратегій потрібно покращити розуміння патофізіологічних механізмів післяопераційного болю.

КЛЮЧОВІ СЛОВА: лікування болю, післяопераційний біль, невідкладна хірургія.

Introduction

Non-traumatic emergency general surgery involves a heterogeneous disease spectrum and a varied that may present with several underlying diseases [1]. In the last decades, this cohort of patients has progressively included more vulnerable, frail, and elderly people. Hypovolemia, hypoxia, sepsis, and most often severe pain are frequent, and the perioperative treatment may be challenging [2]. The surgical treatment should be supplemented by high-quality perioperative care, ideally performed by multidisciplinary teams trained to identify and handle complex postoperative courses [3]. Acute postoperative pain (APP) is still a major burden for most healthcare systems. About 70 % of the 240 million postsurgical patients every year suffer from moderate-to-severe pain [4]. Uncontrolled APP may result in significant clinical and psychological changes that may be associated with higher subsequent risk of several medical complications due to immobility, poor respiratory mobility, and failure of nutritional progress, including pneumonia, infections, deep vein thrombosis, cardiovascular events, and depression [5]. Pain relief is fundamental in multimodal strategies to improve surgical outcome, together with preoperative assessment, information and optimization, reduction of surgical stress, rapid mobilization, and early oral nutrition [6]. The APP management may be pursued by several professionals and in many places a multidisciplinary team is not available. For this reason, precise indications must be provided to physicians managing postsurgical patients and specifically to emergency general surgeons to implement their tools in assisting emergency surgical patients.

International and national guidelines recommend in case of moderate-to-severe pain a few analgesic techniques, including intravenous (i.v.), per oral (p.o.) or subcutaneous (s.c.) routes, as well as epidural analgesia (EA), patient-controlled analgesia (PCA), and continuous peripheral nerve blocks (CPNB) [7]. Administration may aim for both local pain control and systemic effects, often with a combination to achieve optimal results. While an appropriate pain management has been optimized in the perioperative pathways after elective surgery, the traditional perioperative treatment of patients undergoing emergency surgery is often a non-standardized practice [8]. Several specific conditions may warrant a customized approach, including the presence of sepsis and infection, contamination at local sites and the type of intervention done

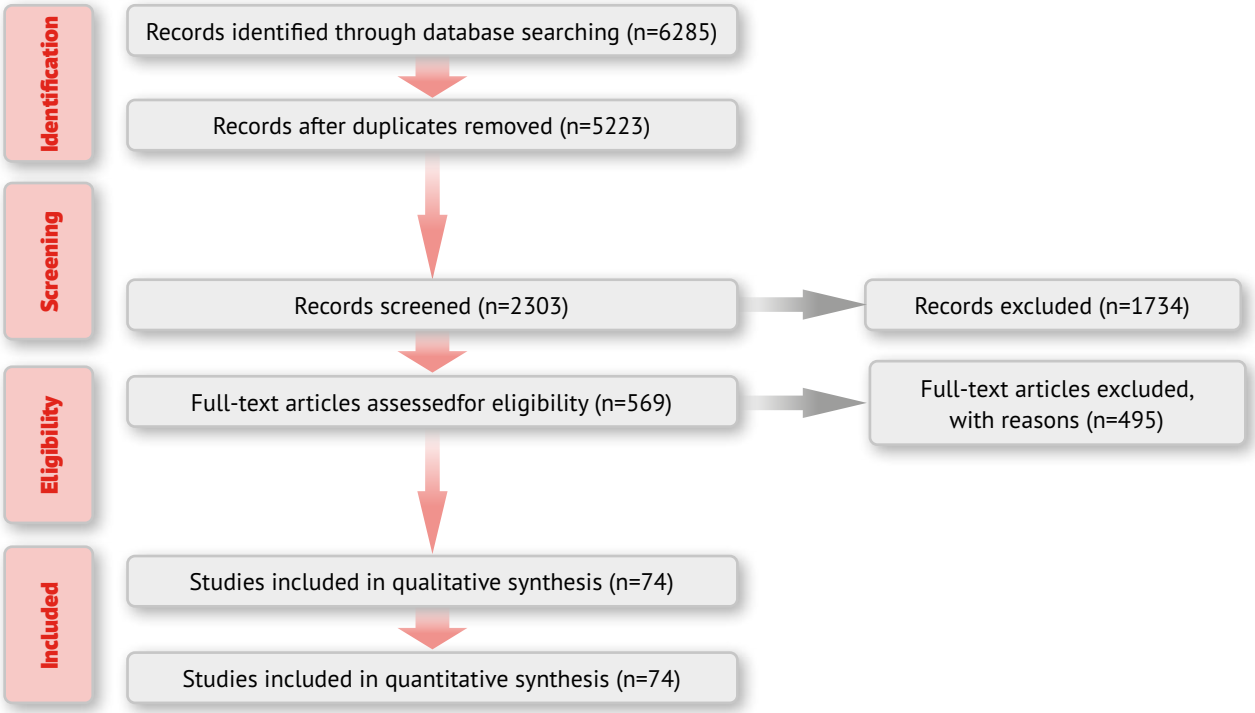

Fig. PRISMA flowchart

or planned for the specific condition at hand. The common major emergency procedures and their consequences represent a massive healthcare burden, and there is tremendous potential for quality improvement [9].

Some recent data support the use of artificial intelligence (AI) to develop better clinical decision support tools based on machine learning [10]. Some studies tried to move from patient-controlled analgesia to AI-assisted patient-controlled analgesia [11].

The aim of the present guidelines is to suggest the appropriate pain management after non-traumatic emergency surgical intervention and to give to surgeons and physicians working in different settings a list of indications in order to prescribe the best analgesia possible in the absence of a multidisciplinary pain team. Four international recognized scientific societies: World Society of Emergency Surgery (WSES), Global Alliance for Infection in Surgery (GAIS), Italian Society of Anesthesia, Analgesia Intensive Care (SIAARTI), and American Association for the Surgery of Trauma (AAST), participated in the project and approved the final manuscript.

Materials and methods

The bibliographer conducted a computerized search in different databases (MEDLINE, PubMed, Scopus, Web of Science, Embase). Citations were included up to June 2021 using the primary search strategy: acute postoperative pain, emergency surgery, pain assessment, acetaminophen, NSAIDs, ketamine, opioids, epidural anesthesia, peripheral nerve blocks, continuous wound infusion, local infiltration combined with AND/OR with synonyms and MeSH terms. We considered acute pain management after major abdominal pathology requiring urgent emergency laparotomy or laparoscopy, including reoperations after elective gastrointestinal surgery and reoperations after previous abdominal surgery. No language restriction was imposed. Duplicates and animal studies were removed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conferences, comparative studies, congresses, guidelines, government publication, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, and randomized controlled trials. Narrative review articles were also analyzed to identify other studies. Abstracts were screened, and irrelevant studies were removed; then, a full-text assessment of the articles was performed. Case reports were excluded. In case of disagreement between the two reviewers (FC and FCo), the consensus was reached by discussion. If there was no consensus, another two reviewers were sought (FCa and FFo). PRISMA guidelines flowchart [12] is reported in fig. Level of evidence (LoE) was graded in high, moderate, low, and very low. The grade of recommendation (GoR) graded as strong, moderate, and weak was calculated, keeping into consideration the GRADE model [13]. An international expert panel discussed the different issues in subsequent rounds. At each round, the manuscript was revised and improved. The final version about which agreement was reached resulted in the present manuscript.

Notes on the use of the guideline

These guidelines present evidence-based methods for optimal management of acute postoperative pain management in emergency general surgery patients. The practice indications which were promulgated in this work do not represent a standard of practice. These are suggested plans of care based on the best available evidence and experts' consensus, but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given medical management method, which method should be finally determined by the treating health care provider after considering the conditions

at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. However, the treatment results' responsibility rests with those directly engaged and not with the consensus group.

Pain assessment and management

Statements

- Postoperative pain must be recognized and treated as soon as possible and as best as possible in all patients (high recommendation, intermediate quality evidence).
- Emergency general surgery may be associated with more severe postoperative pain; specific attention should be given to this patient group (GoR 2, LoE B) (moderate recommendation, intermediate quality evidence).
- Postoperative pain assessment, at rest and – if possible – on movement, is strongly recommended, to improve patient management after emergency surgery (moderate recommendation, intermediate quality evidence).
- Preemptive analgesia is a viable option in reducing postoperative opioid consumption (GoR 2, LoE B) (moderate recommendation, intermediate quality evidence).
- Adequate education for the patient and, if possible, of the family about the surgical and anesthesiologic treatment, options, plan, and aims of pain management should be performed whenever it is possible (GoR 1, LoE B) (high recommendation, intermediate quality evidence).
- Perioperative pain management should be implemented considering patient history, comorbidities, ongoing chronic therapy, and potential risk for substance abuse (GoR 1, LoE B) (high recommendation, intermediate quality evidence).
- Validated pain scales should be included into treatment planning, ongoing evaluation, and adjusting process (GoR 1, LoE B) (high recommendation, intermediate quality evidence).
- Pain management should be adjusted to ensure the greatest effect and the lowest side effects possible (GoR 1, LoE B) (high recommendation, intermediate quality evidence).

Emergency general surgery (EGS) is related to a worse acute postoperative pain compared to elective surgery [14-18]. Patient- and family-centered education is regarded as very important during the preoperative and postoperative periods [14, 15, 17, 19-22]. Telling patients how a drug is chosen, its properties and effects, understanding its side effects, and shared in the decisions helps reduce APP. A recent study proved that a lower educational level worsens pain [23].

An accurate evaluation including psychiatric comorbidities, namely dementia and delirium, may facilitate APP management since pain assessment techniques in these conditions may be much more time-consuming [19, 21, 24]. Assessment tools that incorporate a behavioral component for pain scoring have demonstrated validity in patients with dementia [25]. Special attention should be paid to the treatment of anxiety [26], evaluation of depression [26], and catastrophizing [15, 17]. Uncontrolled pain syndrome is manifested by tachycardia, arterial hypertension, increased rigidity of the muscles of the anterior abdominal wall and chest muscles, which leads to alteration of the ventilation and hypoxemia, difficulties in coughing and definitively to an increased risk of respiratory infectious complications. Enhanced sympathetic stimulation inhibits peristalsis and at the same time increases the tone of the smooth muscles of the intestine, which is fraught with the development of postoperative paresis. In addition, postoperative pain syndrome prevents early mobilization of patients and also contributes to their emotional and physical suffering, sleep disturbances. A sudden increase in pain, especially associated with the appearance of tachycardia, hypotension, hyperthermia, requires an urgent comprehensive assessment of the patient's condition, since this may be a harbinger of postoperative complications (bleeding, anastomotic leaks, deep vein thrombosis, etc.).

All these conditions may contribute to worsening APP outcome. Coping strategies could be used specially to contrast catastrophizing thoughts.

The assessment of preoperative chronic pain is necessary because it is demonstrated that previous chronic pain history since may be associated to a worse APP [22]. Moreover, high APP pain level may lead to persistent postoperative pain [16, 17, 19, 20, 22, 27].

Accurate APP's assessment, which is essential, is usually underestimated, underevaluated, and underperformed [14-16, 18, 20, 21, 23, 24, 28-32]. Some tools such as visual analog scale (VAS) score for some aspects seem to be inappropriate in measuring APP since it does not give a multidimensional pain evaluation. Hence, predictor index or questionnaire should be adopted to give the best APP evaluation.

Consideration should be given to APP follow-up evaluation and adequate therapy during the postoperative period. In fact, pain drugs are often administered not at regular intervals [18, 33] nor according to pain scales [15, 18, 33]. Local policy must include standard interval at which a patient is assessed and reassessed for pain. After a pain intervention is completed, reassess patients for both pain control and adverse reactions to the intervention at an appropriate interval based on the anticipated effect. When a significant change in worsening pain level is reported, reevaluate the patient for possible postoperative complications. A combined nurse service with clinician supervision seems to provide better outcomes in APP management [14, 15, 18, 20, 21, 23, 24, 34, 35]. It is proven that 24 h/day monitoring with a regular assessment/documentation guarantees a better pain treatment [14, 20].

In addition to psychiatric comorbidities, chronic pain, and patient dealing with substances of abuse, special attention should be paid to OSAS patients, since a correlation with APP is not fully understood [36, 37]. In this category of patients, antalgic therapy recommendation aims to reduce as much as possible the use of opioids to prevent possible cardiopulmonary complications. Furthermore, literature advises to be aware of age, body mass index (BMI) and gender: Younger age [16, 18, 23] and female gender [16, 18, 33] could be risk factors for APP. Some studies show that low BMI is associated with better pain outcomes [37]. Also knowing about the patient's smoking habits could improve APP [23].

Preemptive and preventive NSAIDs seem to reduce both pain and morphine use. Clinically significant adverse events from nonsteroidal anti-inflammatory drugs (NSAIDs) administered before surgery are possibly under-reported; for this reason, it is impossible to define with high level of evidence the safety of either preemptive or preventive NSAIDs [38].

Non-opioids drugs

Statements

- Opiates usage should be reduced as much as possible in postoperative pain management strategies (strong recommendation, intermediate quality evidence).

- Multimodal pain management should always be considered to improve analgesia while reducing individual class-related side effects; a pharmacological step-up approach including major opiates when necessary should be adopted (strong recommendation, intermediate quality evidence).
- Whenever contraindications are absent, acetaminophen, NSAIDs (strong recommendation, high-quality evidence), and gabapentinoids administration (moderate recommendation, moderate quality evidence) are recommended in multimodal analgesia.
- Acetaminophen administered at the beginning of postoperative analgesia may be better and safer than other drugs (strong recommendation, intermediate quality evidence).
- Acetaminophen used in multimodal and preemptive therapy is associated with a reduction of opiates side effects and improved postoperative outcomes (strong recommendation, intermediate quality evidence).
- Coxib administration may be considered if there are no contraindications (strong recommendation, moderate quality evidence).

Multimodal analgesia involves the use of different classes of analgesic medications (NSAIDs, COX2 inhibitors, gabapentinoids, or acetaminophen in combination with morphine IV-PCA) with different mechanisms of action on the peripheral and/or central nervous system.

The different combinations of these drugs lead to additive or synergistic effects on pain relief and can potentially reduce the side effects of mono-modal interventions. The drugs used for this purpose include:

- Acetaminophen (paracetamol): it is effective as an analgesic mainly if used in combination with NSAIDs or morphine. Its use reduces opioids use [39-41].
- NSAIDs: are indicated for the treatment of moderate pain when used alone. Their use in multimodal analgesia reduces morphine consumption and related side effects [40].
- Opiates: are the first-line therapy to treat pain in these patients. They also reduce anxiety and dyspnea [42, 43]. PCA is recommended when iv route is needed in patients with adequate cognitive functions, starting with bolus injection in opioid naïve patients [7].
- Gabapentinoids such as gabapentin and pregabalin can be considered as a component in multimodal analgesia. They act by decreasing the release of neurotransmitters in the synapse, thus providing a nociceptive blocking activity.
- Alpha-2-agonists: in addition to their anti-hypertensive effect, they have been shown to have a sympatholytic effect by inhibiting norepinephrine release, thus reducing the opiates requirements.

Acetaminophen in a multimodal regimen is a valid and effective option. A study conducted in nearly 800,000 patients undergoing common major surgical elective and emergency procedures showed that this drug in a multimodal therapy regimen provides a cost-effective strategy to improve outcomes and patient satisfaction with a side-effect profile that is superior to opioids alone in moderate–severe APP [44]. The use of acetaminophen is associated with shorter length of stay, decrease in opioid-related complication rates, and lower costs in a heterogeneous population of patient who underwent to elective and emergency cardiovascular, colorectal, general, obstetrics and gynecology, orthopedics, or spine surgery [45]. A case-control cohort study of 1231 patients undergoing gynecologic and abdominal surgery showed that ibuprofen and acetaminophen (600 mg every 6 h and 500 mg every 6 h) could offer an adequate postoperative pain control with a supply of opioids (hydrocodone or oxycodone) if needed [46]. A single study suggests the use of IV acetaminophen in the beginning of postoperative analgesia since its antalgic properties are better and safer than IV tramadol in patients undergoing laparoscopic cholecystectomy [47].

Different efficacy can be assessed according to the timing in the administration of acetaminophen, in the context of multimodal analgesia, as a preemptive analgesia. Acetaminophen used in multimodal and preemptive therapy (1 g before laparotomy with naproxen 250 mg and pregabalin 150 mg) was associated with a reduction of opiate side effects as well as a fewer length of stay, lower opioid-related complication rates, and lower costs compared to patients who had not received this treatment [48].

Intravenous acetaminophen (i.v. acetaminophen every 6 h from 6 h after surgery up to 72 h) can be associated with thoracic epidural anesthesia (TEA); a study has been shown to provide a superior postoperative pain management compared to TEA alone in a randomized controlled trial with 120 patients who underwent distal gastrectomy [49].

Caution is needed in the frail patient, especially in the context of coexisting liver disease. For an amount of acetaminophen infusion sufficient to ensure a significant reduction in postoperative pain compared with groups without treatment ($p=0.008$), an increase in alanine aminotransferase has been observed ($p=0.043$) [50].

Perioperative NSAIDs utilization results regarding the reduction of hospital stay and lowering morbidity have been demonstrated in elective surgery [51]. The literature suggests a potential correlation with dehiscence, technical failures, and wound healing inhibition in emergency general surgery patients with colon or rectal anastomoses [52]. There is not enough evidence to establish the effectiveness of NSAIDs beyond their safety profile.

In terms of efficacy for the individual NSAID drugs, no direct comparisons trial is available. Effectiveness analysis was conducted on the single NSAID once at a time. In the case of abdominal emergency surgery, it was found that perioperative administration of Ibuprofen IV 800 mg every 6 h decreased morphine requirements and pain score and it has been found safe and well tolerated [53]. The literature might suggest also considering the use of HP×CD-diclofenac in a multimodal approach to analgesia. HP×CD-diclofenac in postoperative setting reduces postoperative opioid requirements during the whole postoperative course (all $p<0.005$ vs placebo) [54]. The combination of NSAIDs with acetaminophen improves the quality of pain relief compared to the appointment of each of the drugs separately [55].

The use of coxib is effectiveness in a major surgery context [56, 57] since it provides analgesia and opioid-sparing effects in the 2-3 days immediately following major gastrointestinal surgeries employing laparotomy and reduces the VAS scores both at rest and with movement, reducing also opioids adverse effects in patients following liver resection. A word of caution must be spent regarding the associated use of coxib and NSAIDs as their combination seems to increase the incidence of myocardial infarction and to affect kidney function [58, 59].

Results about the use of *gabapentinoids* in postoperative management in EGS are heterogeneous and conflicting [60].

Preemptive anesthesia with other medications such as gabapentinoids to treat postoperative pain could lower opioid consumption and pain scores.

Due to the paucity of the literature, it is not possible to provide specific indications for the use of *ketamine* in emergency abdominal surgery. According to the literature, a single dose or infusion of ketamine appears to reduce pain score, and opioid consumption in the 48 h following surgery, especially in patients who have undergone major chest, abdominal, and orthopedic surgery [61-63]. Evidence is reported from various types of surgery, including abdominal surgery, on the administration of ketamine added in an opioid intravenous patient-controlled analgesia (IV-PCA) with a reduction in pain, opiate consumption, and PONV up to 24-72 h after surgery [64, 65]. Ketamine is recommended in severe pain management, and subanesthetic doses considered to have evidence of efficacy in acute pain are boluses <0.35 mg/kg and infusions at 0.5-1 mg/kg/h, with no intensive monitoring required [61]. The recommended dose in severe APP management using an IV-PCA is 1-5 mg. It should not be used in uncontrolled cardiovascular disease, pregnancy, active psychosis, severe liver dysfunction, high intracranial, and ocular pressure [61]. A prospective cohort study shows that perioperative adding of ketamine IV (0.25 mg/kg bolus followed by 0.25 mg/kg/h, maximum 1 mg/kg) to opioids did not improve postoperative pain after colorectal surgery perception nor decrease morphine equivalents maybe due to an inappropriate dose compared to bupivacaine 0.0625 % and fentanyl 2 μg/ml [66].

The use of dexmedetomidine in major abdominal surgery can be considered. Dexmedetomidine in combination with fentanyl-based intravenous PCA (dexmedetomidine infusion rate: 0.07 μg/kg/h with a bolus dose of 0.007 μg/kg, and fentanyl infusion rate: 0.3 μg/kg/h with a bolus dose of 0.03 μg/kg allowed every 15-min lockout time) had the same antalgic effects of patient-controlled epidural analgesia (PCEA) without hemodynamic instability and with a less invasive technique [67]. However, no precise indication can be given for patients undergoing emergency abdominal surgery.

Opioid drugs

Statement

- In the treatment of moderate-to-severe pain, unresponsive to other medications and in which regional anesthesia techniques are not indicated, the use of major opiate is indicated (strong recommendation, moderate quality evidence).
- Initial infusion of opioids using intravenous patient-controlled analgesia should be avoided in opioid naïve patients (strong recommendation, moderate quality evidence).
- Sedation levels, respiratory status, and the possible development of adverse events in patients on systemic treatment with opioids must be regularly assessed (strong recommendation, weak quality evidence).
- If indicated, infusion of opiates using intravenous patient-controlled analgesia should be preferred to spinal patient-controlled analgesia in postoperative pain management whenever the intravenous route is viable (strong recommendation, moderate quality evidence).

Opioids are strong and fast acting analgesics that are very effective and convenient in use for severe APP. Unfortunately, opioids are also associated with an important side effect and the risk of drug dependency. We are now facing a worldwide opioid crisis that causes 22,000 deaths annually in the USA alone. Although opioids have a central place in management of severe APP, it is therefore important to select an appropriate opioid for a time period as short as possible.

The use of PCA with major opiates after EGS is effective and useful [68]. Although the literature confirms the superiority of treatment for severe APP with opiates PCA, there is no clear evidence about which opiate drug should be preferred. Morphine, which is by far the most widely used drug, is not the ideal molecule as it has high renal clearance with potential accumulation and adverse effects [69, 70]. The alternatives are fentanyl, oxycodone, and sufentanil. As regards the type of molecule to be used, the literature does not exclusively address an opiate: oxycodone (0.7 mg/kg – background continuous infusion of 1 to 2 mL/h 1 mL bolus with a 15-min lockout) is comparable to fentanyl (fentanyl 12 mg/kg – background continuous infusion of 1 to 2 mL/h 1 mL bolus with a 15-min lockout) in the relief of postoperative pain following laparotomy. Oxycodone only seems to provide a slightly better postoperative pain relief and less sedation, but it is also associated with more side effects than fentanyl [71]. No significant pain scores differences at 5 and 30 min postoperatively were registered between oxycodone and fentanyl treatment in patients undergoing laparoscopic cholecystectomy [72]. The use of sublingual sufentanil tablet system has been compared to PCA. Sufentanil seems to be an appropriate choice due to its high affinity for the μ opioid receptor, its high therapeutic index, and the absence of clinically relevant active metabolites [4]. The sublingual sufentanil tablets (SSTs) is a noninvasive combination of a drug and a medical device which contains a cartridge of 40 tablets (sufentanil 15 μg) with a lockout interval of 20 min that seems to have better safety and tolerability in patients with open abdominal surgery or major orthopedic surgery [73]. In open abdominal surgery, SST 30 mcg is effective for the management of moderate-to-severe postoperative pain [74]. The literature regarding SST administration in EGS is scarce, so no definitive indication can be given.

In some context, opiates are rarely given during the postoperative period to treat moderate-to-severe acute pain (13 %, while other analgesics were administered in the 86.4 %) [75]. However, in perioperative conditions of moderate-to-severe pain unresponsive to other treatment opioids represent a viable and effective option. Side effects of opioid analgesics are dose-dependent, and at high doses, they can induce hyperalgesia [76].

Whenever PCA is not available or cannot be administered due to due to clinical or social barriers, transdermal fentanyl patch (25 μg/h) may be used. These patches should be affixed 12-14 h before surgery and avoid the continuous IV infusion of fentanyl after surgery. Transdermal administration is shown to reach a higher constant concentration without any evidence of respiratory depression [77]. There are no differences in pain score between transdermal fentanyl patch and IV fentanyl and the use of rescue analgesics after laparoscopic cholecystectomy [77].

Route of drugs administration

Statement

- Oral administration of analgesic drugs should be preferred over intravenous route whenever feasible, and drugs absorption may be reasonably warranted (strong recommendation, moderate quality evidence).
- The intramuscular route should be avoided in postoperative pain management (strong recommendation, moderate quality evidence).
- Epidural and regional anesthesia is recommended in emergency general surgery, whenever feasible and if not delaying the emergency procedures (intermediate recommendation, intermediate quality evidence).
- Neuraxial administration of magnesium, benzodiazepines, neostigmine, tramadol, and ketamine should be avoided (strong recommendation, moderate quality evidence).
- Patients with neuraxial anesthesia must be monitored and assessed adequately (strong recommendation, low quality evidence).

Available evidence suggests that intravenous administration of opioids or NSAIDs is not superior for postoperative analgesia compared with oral administration. Emergency abdominal surgeries usually affect the ability to take medications orally or enterally. Moreover, drug absorption after oral administration is a highly complex process, depending on both physicochemical properties of the drug and physiological conditions of the body. Postoperative ileus is an inevitable consequence of abdominal surgery caused by pharmacological agents (anesthetics, opioids) in the perioperative period, neural mechanisms, and intestinal inflammation due to the manipulation during the surgery – which is the most important pathophysiological mechanism. In emergency conditions, inflammatory cascade of events leads to a higher inflammatory background [15].

Furthermore, drugs are absorbed in unionized state, which is dependent upon GI pH; also, the changing of gastric emptying rate and intestinal transit time can affect drug absorption. The perioperative period after major abdominal surgeries is characterized by a slower gastric emptying rate with a higher risk of aspiration and an impaired intestinal transit time. For these reasons, the oral route of administration is frequently not suitable in the acute postoperative.

Oral medication in an acute postoperative setting could be administered before surgery – in a preventive way – or in the postoperative period through the sublingual route.

PCA showed a better pain relief in abdominal surgery compared to intravenous morphine continuous infusion (2 mg/h as basal infusion and 3-5 mg IV bolus administration every time when required to obtain NRS below 3/10) [78]. Patient-controlled analgesia (PCA) either intravenous or epidural provides superior postoperative pain control and patient satisfaction, even if it increased amount of opioid consumption [79].

A study has tried to confirm this by correlating EA and reduced complications after colectomy and support a possible role for epidural analgesia in a multimodal analgesic regimen after open colectomy [80]. Emergency colorectal resection for colorectal cancer in colonic obstruction without peritonitis and in patients with elective surgical intervention can be considered similar. For this reason, the approach in pain management can be mutualized from literature evidence obtained in elective patients. One main point to be considered is the cautious usage of opiates in those patients who may present dynamical ileus due to intestinal overdistension. These patients may have difficulties in recovering intestinal motility, and opiates may exacerbate the ileus.

Thoracic epidural analgesia (TEA) use has been associated with a lower incidence of paralytic ileus, attenuation of the surgical stress response, improved intestinal blood flow, improved analgesia, and reduction of opioid use [81]. PCEA is suggested in fragile patients because this approach would seem to decrease stress response and minimize immune dysfunction improving plasma cortisol (Cor), interleukin (IL)-6 and IL-17 levels, and helper T-cell differentiation in esophageal carcinoma patients. PCEA stress response effects are most pronounced upon combination TEA/PCEA treatment [82]. On the other hand, in the elderly patient, as in the young patient, this type of analgesia was associated with more frequent episodes of numbness and motor weakness/deficits, hypotension, and nausea/vomiting comparing it to morphine PCA. Therefore, a retrospective analysis suggests using different PCEA strategies of administration regimens or adverse effects prevention for young and elderly patients [83]. We also suggest caution in males who underwent EA because of the possibility of urinary retention which slows patient recovery and may impair renal function. Urinary retention after EA had a higher incidence, and routine transurethral bladder drainage with early removal to prevent urinary tract infection is suggested [84].

TEA for pain management in APP seems to be useful also in emergency major abdominal surgery. The most part of the literature showed benefits in oncological elective surgery [51, 85, 86].

TEA does not exclude a multimodal approach, for example, in combination with intravenous acetaminophen. It seems to provide a superior postoperative pain management compared with TEA alone [49]. The type of drug infused and its concentration to provide a differential sensory block with the same effectiveness have been evaluated. Both epidural infusions of 0.125 % ropivacaine with 1 μg/ml fentanyl and 0.125 % bupivacaine with 1 μg/ml fentanyl in major abdominal surgery showed the same antalgic effect with minimal motor block [87]. A prospective randomized study showed that ropivacaine with nalbuphine is more effective than ropivacaine with butorphanol for immediate postoperative pain relief in patients undergoing emergency exploratory laparotomy [88].

Perioperative nerve block and local infiltration

Statement

- Regional anesthesia techniques are effective in both adults and children in site-specific surgery (strong recommendation, high-quality evidence).
- Abdominal wall blocks can be considered a technique with an opioid-sparing effect (intermediate recommendation, intermediate quality evidence).
- Transversus abdominal plane (TAP) block in patients undergoing laparoscopic abdominal surgery is proved to be a safe and effective method to treat postoperative pain (intermediate recommendation, intermediate quality evidence); a rectus sheath block is a viable alternative to the TAP block (intermediate recommendation, intermediate quality evidence).
- Local wound infusion is suggested as a component of multimodal analgesia (weak recommendation, moderate quality evidence).

- The use of continuous local wound infusion catheters is associated with a significant decrease in visual analogue scores for pain at rest and with activity (weak recommendation, intermediate quality evidence).
- Use of continuous local wound infusion catheters consistently reduces the need for opioids, both as rescue and total dose (weak recommendation, intermediate quality evidence).
- A pre-peritoneal catheter is not associated with an increased risk of surgical site infection (weak recommendation, intermediate quality evidence).
- Pre-peritoneal catheters must have a planned removal process including institution of appropriate analgesia (moderate recommendation, intermediate quality evidence).

The use of perineural/local analgesia techniques is indicated in case of major interventions characterized by moderate-to-severe pain (NRS >6) affecting the chest and abdominal wall [89]. The most frequently used peripheral nerves block (PNB) is the use of the rectus sheath block and the transversus abdominis plane (TAP) block. Regarding the timing of the block, it is suggested to perform rectus sheath block before surgery in pain management for laparoscopic abdominal surgery [90].

TAP block in patients undergoing laparoscopic abdominal surgery is proved to be a safe and effective in treating postoperative pain with a statistically significant decrease in VAS at 12 h after the surgery [91, 92].

As far as the use of adjuvants is concerned, there is evidence in the literature suggesting the use of perineural dexamethasone with ropivacaine for thoracic paravertebral block in patient undergoing thoracotomy since it improves postoperative analgesia quality. NRS scores, rate of analgesic usage, ambulation time, and intestinal function recovery time were significantly reduced in patients with local wound infusion (LWI) compared to placebo at each postoperative time point (6, 12, 24 and 48 h; $p<0.05$). And the NRS scores of patients with LWI at 12 h post-surgery were significantly reduced compared with the PCA group ($p<0.05$) [93, 94].

Local anesthetics would directly block transmission of pain from nociceptive afferents from the wound surface; local anesthetic may also inhibit local inflammatory response to injury [95].

Postoperative pain management associated constipation

Constipation does not affect everyone who has surgery, but it is a relatively common side effect of pain medications, anesthesia, and a lack of mobility. The anesthetic regimen administered during surgery is likely to have an effect on constipation during recovery. Both the type of anesthesia and the surgical duration affect the likelihood of postoperative constipation. Surgeries that last longer in duration tend to be associated with a higher predisposition to constipation. Post-surgery constipation is often a result of opioid pain medications; given either as part of the anesthesia or for pain relief following the surgery, opioid-induced constipation (OIC) in patients receiving opioids is persistent and the most frequently reported side effect [96, 97].

Multimodal analgesia combines regional analgesia, non-opioid analgesics [acetaminophen, nonsteroidal anti-inflammatory drug (NSAID) or cyclooxygenase (COX)-2 specific inhibitor], lidocaine infusions, gabapentinoids, and ketamine. Numerous studies have shown the opioid-sparing effect of this approach resulted in an accelerated GI recovery and improved outcomes. However, an optimal combination of these elements has not yet been elucidated [98, 99].

Caffeine is widely known as a stimulant to colonic motor activity in animals and humans. Clinical trials have shown that caffeinated drinks decrease the time to flatus and first bowel movement and if given as soon as 2 h after surgery, it may accelerate GI recovery and reduce LOS [100, 101].

Lastly, the use of regional anesthesia over general anesthesia whenever possible may help in reducing the number of drugs used and thus may reduce the likelihood of constipation after surgery.

Patients not amenable for interventions or already operated but not suitable for further interventions to manage affecting disease or complications

Unlike patients with treatable conditions or where active organ support is chosen for their care, there remains a group of frail patients or those for whom surgical intervention would be non-beneficial and there is a defined role for analog-sedative medications in the treatment of this cohort.

Pain assessment

- Periodic assessment of pain score is mandatory using validated systems to evaluate the response to treatments and to allow adjustments (strong recommendation, intermediate quality evidence).
- Observational pain scales are less reliable than patient reported metrics. However, in the non-communicative patient, observational pain scales should still be applied (strong recommendation, low quality evidence).

Different pain assessment tools have been validated: NRS (Numeric Rating Scale), VAS (visual analog scale) and VRS (Verbal Rating Scale) or the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CCPOT) in case of critically ill patients. There is no evidence of the superiority of one specific tool, and the choice should be made according to patient status (developmental, cognitive, educational, cultural status, and language differences). It remains that patient self-assessment of pain is the most valuable tool. Patient's opinion must be listened and his/her feelings trusted [102-104].

Drug therapy

- Multimodal analgesia is suggested to treat moderate-to-severe pain in patients not amenable for surgical interventions or already operated on but not suitable for further interventions (strong recommendation, intermediate quality evidence).
- The combination of systemic multimodal analgesia with regional analgesia is suggested in patients already operated on but not suitable for further interventions (strong recommendation, intermediate quality evidence).
- Patients not amenable for surgical interventions or already operated on but not suitable for further interventions should be considered for palliation to achieve the control of all other related symptoms such as nausea, vomiting, dyspnea, agitation, and delirium (strong recommendation, intermediate quality evidence).

In patients not suitable for further intervention due to the clinical conditions or due to the disease itself, multimodal analgesia is effective and should be adopted in postoperative pain management. The different combinations of the known drugs with their additive or synergistic effects on pain relieve reduce the side effects of mono-modal interventions and increase the effect on pain reduction (table 1).

Table 1. Initial opioids titration in opioid-naive patients during palliate care

Drug	Frequency	Intravenous or subcutaneous	Oral
Morphine	8/24 h	2.5-10 mg	2.5-10 mg
Fentanyl	8/24 h	25-100 mcg	Not available

Nausea and vomiting

- Nausea and vomiting should be managed with medications that target dopaminergic pathways (i.e., haloperidol, risperidone, metoclopramide, prochlorperazine) (high recommendation, intermediate quality evidence).
- Octreotide should be utilized in the treatment of nausea and vomiting due to bowel obstruction caused by cancer (high recommendation, intermediate quality evidence).
- We suggest adding a second agent (i.e., ondansetron) to control nausea and vomiting when the first-line medications are unable to control the symptoms (high recommendation, intermediate quality evidence).

Aforementioned drugs are routinely used as therapies for nausea because of their inhibition of receptors in the brain's chemoreceptor trigger zone. Studies have not shown newer 5-HT3 medications to be superior to older dopaminergic agents in treating nausea at the end of life [105-108].

All medications that may be added as second agent in treating refractory nausea are listed in table 2 together with the setting of use and doses and route of administration.

Delirium

- Whenever appropriate, the evaluation of delirium should be done using standardized assessment tools validated in critically ill patients like Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) (high recommendation, intermediate quality evidence).
- Possible causes of delirium, including drug-induced delirium, must be minimized, and pain control should be optimized before the pharmacological approach is implemented (high recommendation, intermediate quality evidence).
- The use of i.v. haloperidol or droperidol in hyperactive (RASS +1/+4) or hypoactive (RASS 0/-3) delirium with or without hallucinations is recommended (intermediate recommendation, intermediate quality evidence).

Delirium is common in the last weeks/days of life, so it must be considered in every patient in palliative care showing a change in behavior. Symptoms can affect different areas of cognition (memory, orientation, language, visuospatial ability, or perception) and may include hallucinations and disturbances in the sleep – wake cycle and can cause distress in both the patients experiencing it and those around them (DSM-5 [109]). Validated tools have been developed to allow screening of delirium to help non-specialists to address a diagnosis [110, 111].

Reversible causes account for 30-50 % cases of delirium, especially drugs and poorly controlled pain. Drugs potentially responsible for delirium include benzodiazepines, corticosteroids, anticholinergics, opioids, and other drugs with psychoactive properties. Other possible reversible causes are metabolic disturbances (electrolyte imbalances, dehydration, hypo- or hyperglycemia), hypoxia, anemia, sepsis [112].

Overall, only 50 % of delirium cases are reversible. The other half requires medical management which focuses on reducing agitation and perceptual abnormalities. Haloperidol is the drug of choice in the pharmacological treatment of delirium. An initial dose of 0.5-2 mg in. slow iv bolus may be used off-label. Haloperidol is associated with extrapyramidal side effects and lengthening of QT [110, 111].

Dyspnea

- The assessment of respiratory distress should be done using a standardized assessment tool and the presence of suggestive objective signs. We recommend a stepwise approach to the treatment of dyspnea (high recommendation, intermediate quality evidence).
- When death is not imminent, the treatment of the etiology of dyspnea is recommended (high recommendation, intermediate quality evidence).
- Noninvasive ventilation to control dyspnea is suggested only until a properly deep sedation is reached or when sedation is inadequate. We recommend noninvasive

Table 2. Additional agents for the treatment of nausea and vomiting

Drug	Setting	Frequency	Intravenous or subcutaneous	Oral	Topic
Scopolamine	Increased oral secretions	1/72 h	–	–	1.5-3 mg
Lorazepam	Anticipatory nausea	4/24 h	0.5-2 mcg	0.5-2 mcg	–
Dexamethasone	Bowel obstruction Intracranial hypertension	3-6/24 h	2-8 mg	2-8 mg	–
Haloperidol	Nausea	3-6/24 h	0.5-2 mg	0.5-2 mg	–
Prochlorperazine	Nausea	3-4/24 h	5-10 mg	5-10 mg	–
Chlorpromazine	Nausea	3-4/24 h	12.5-25 mg	25-50 mg	–

ventilation only in predisposed settings with trained medical staff (high recommendation, intermediate quality evidence).

- Opioid usage as first-line treatment for dyspnea is recommended (high recommendation, intermediate quality evidence).

Dyspnea is the subjective awareness of altered respiratory function which usually results in respiratory distress. Respiratory distress is the totality of behavioral modifications that can be observed and measured (use of respiratory accessory muscles, nasal flaring, tachypnea, tachycardia, paradoxical breathing, fearful facial expression). Dyspnea is usually present in dying patients. When possible, being a subjective symptom, it must be assessed directly with the patient using standardized assessment tools [110].

The use of non-medical strategies to decrease respiratory distress should be considered like optimal positioning in sitting position, increased ambient air flows, use of fans, cold air. Noninvasive ventilation techniques as oxygen therapy include high-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) ventilation to relief or mitigating dyspnea [110] by reducing the work of breathing in the absence of formal contraindication (intestinal occlusion and vomiting). Aspiration of airways if rattle is present. Anti-secretory medications may or may not be useful or required to decrease pulmonary secretions [113, 114].

Sedation with benzodiazepines or propofol can be considered as second line if dyspnea is not resolved with adequate doses of opioids since fear and anxiety can be con causes of the dyspnea in the dying patient [115].

Conclusions

Dealing with acute postoperative pain in the emergency abdominal surgery setting is complex, requires special attention, and should be multidisciplinary. Several tools are available, and their combination is mandatory whenever is possible. Analgesic approach to the various situations and conditions should be patient based and tailored according to procedure, pathology, age, response, and available expertise. A better understanding of the patho-mechanisms of postoperative pain for short- and long-term outcomes is necessary to improve prophylactic and treatment strategies.

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