Acute pain in the critically ill patient: revisiting the literature

Dor aguda no paciente crítico: revisitando a literatura

Jose Mauro Vieira Junior[1], Laura Herranz Prinz[1]

DOI 10.5935/2595-0118.20220024-en

ABSTRACT

BACKGROUND AND OBJECTIVES: According to the redefinition, acute pain is a somatic experience, with individual perception of physical or existential threat, comprising affective, cognitive and behavioral components. In critically ill patients, pain is a frequent and poorly controlled symptom, causing worse outcomes. The objective of this study was to explore the topic of acute pain in critically ill adult patients, focusing on some aspects of pathophysiology, in addition to updates regarding diagnosis, multimodal therapy and discussion of its control as a marker of good care practice.

CONTENTS: A search strategy was performed with the descriptors previously defined in the Pubmed and Cochrane portals, in the period from 2011 to 2021, without a language restriction filter. Acute pain represents a physiological response to a nociceptive stimulus, with high relevance due to its ability to activate complex pathways (inflammatory, hormonal and immune), with systemic repercussions. Pain assessment is often performed using recognized scales, but with limited validation in patients with traumatic brain injury, burns and patients with severe delirium and/or dementia. Studies considering these patients point to the use of new technologies in an attempt to target this diagnosis, such as bedside pupillometry and the use of platforms capable of integrating multiparametric measurements. Regarding therapy, the concept of analgosedation, aiming at prioritizing analgesia in critically ill patients, presents an approach capable of improving clinical outcomes. In addition, there is a preference for multimodal therapy as a good medical practice through the association of different drugs with different mechanisms of nociceptive blockade as a strategy to achieve pain control and facilitate the reduction of opioid consumption.

CONCLUSION: Due to its systemic effects and prevalence, acute pain is still a relevant problem in intensive care units. New diagnostic methods are being marketed with the aim of targeting this evaluation in complex patients. The approach to acute pain should prioritize the use of multimodal techniques, which present more consistent clinical responses, in addition to reducing the consumption of opioids. The existence of multidisciplinary teams specialized in pain control in the hospital environment is able to assist in difficult cases and help in quality audits.

Keywords: Acute pain, Critical care, Analgesia, Opioids analgesics, Pain management, Quality of health care.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Conforme redefinição, a dor aguda é uma experiência somática, com percepção individual de ameaça física ou existencial, compreendendo componentes afetivos, cognitivos e comportamentais. Em pacientes críticos, a dor representa um sintoma frequente e mal controlado, ocasionando piores desfechos. O objetivo deste estudo foi explorar a temática da dor aguda nos pacientes críticos adultos, com enfoque em alguns aspectos de fisiopatologia, além de atualizações em relação a diagnóstico, terapêutica multimodal e discussão de seu controle como um marcador de boa prática assistencial.

CONTEÚDO: Foi realizada estratégia de busca com os descritores previamente definidos nos portais Pubmed e Cochrane, no período de 2011 a 2021, sem filtro de restrição para idioma. A dor aguda representa uma resposta fisiológica a um estímulo nociceptivo, tendo alta relevância por sua capacidade de ativar vias complexas (inflamatórias, hormonais e imunes), com repercussões sistêmicas. A avaliação da dor é frequentemente realizada através de escalas reconhecidas, porém com validação limitada em pacientes com trauma cranioencefálico, queimados e portadores de *delirium* e/ou demência acentuados. Os estudos considerando esses pacientes apontam para o uso de novas tecnologias na tentativa de objetivar esse diagnóstico, como a pupilometria à beira leito e o uso de plataformas capazes de integrar medidas multiparamétricas. Em relação à terapêutica, o conceito de analgossedação, objetivando priorização de analgesia nos pacientes críticos, apresenta abordagem capaz de melhorar desfechos clínicos. Além disso, há preferência da terapêutica multimodal como boa prática médica através da associação de diferentes fármacos com diversos mecanismos de bloqueio nociceptivo como estratégia para alcançar controle álgico e facilitar a redução do consumo de opioides.

CONCLUSÃO: Por seus efeitos sistêmicos e sua prevalência, a dor aguda ainda é problemática relevante nas unidades de terapia intensiva. Novos métodos diagnósticos estão sendo comercializados com a proposta de objetivar essa avaliação em pacientes complexos. A abordagem da dor aguda deve priorizar o emprego de técnicas multimodais, que apresentam respostas clínicas mais consistentes, além de redução no consumo de opioides. A exis-

Jose Mauro Vieira Junior – https://orcid.org/0000-0002-8607-8145;
Laura Herranz Prinz – https://orcid.org/0000-0002-1944-6980.

1. Syrian-Lebanese Hospital, Education and Research Institute, São Paulo, SP, Brazil.

Submitted on July 21, 2021.
Accepted for publication on April 22, 2022.
Conflict of interests: none – Sponsoring sources: none.

Correspondence to:
Laura Herranz Prinz
E-mail: brasillaura@gmail.com

tência de equipes multidisciplinares especializadas no controle da dor no ambiente hospitalar é capaz de auxiliar em casos difíceis e ajudar nas auditorias de qualidade.

Descritores: Analgesia, Cuidados críticos, Dor aguda, Manejo da dor, Qualidade da assistência à saúde.

INTRODUCTION

In critically ill patients admitted to intensive care units (ICU), pain is a frequent symptom, becoming relevant in daily clinical practice since the decade of 1991[1]. In 1995, the American Pain Society established the symptom as the 5th vital sign and, since then, the need for pain assessment and its better management became a quality measure for medical practice[2]. In addition, despite the current perception of magnitude, pain is still poorly controlled in most ICUs worldwide[3].

By the conceptual redefinition, the acute painful sensation must be interpreted as an individual somatic experience with a perception of threat to physical or existential integrity capable of involving affective, cognitive and behavioral components[4]. In this context, the updated consensus on acute pain management suggests systematic assessment and reassessment, with treatment focused on customization and use of optimized multimodal therapy[5].

The present study's objective was to explore the topic of acute pain in critically ill adult patients, addressing some aspects of pathophysiology, but focusing on updates regarding diagnosis, multimodal therapy and discussion of its control as a marker of good care practice.

CONTENTS

A search strategy was carried out in the Pubmed and Cochrane portals with the following descriptors: "acute pain", "intensive care", "pain management", "opioids" and "quality of care". The references of the included articles were also searched when considered relevant. Articles from 2011 to 2021 were selected, focusing on observational research and clinical trials on the subject, with older articles being accepted if related to the subject of pathophysiology or key publications on the described subject (example: pain assessment with scales). Consensus and reviews on the topic of "acute pain" were also included when published from 2018 onward. No language restriction filters were used.

DISCUSSION

Acute pain represents a physiological response to a nociceptive stimulus and is perceived in the peripheral endings and interpreted in the central nervous system. In addition to neural pathways, pain activates inflammatory pathways and the immune system. The central connections with the hypothalamus promote activation of the hypothalamic-pituitary-adrenal axis, causing hormonal secretion of cortisol, antidiuretic hormone, angiotensin II, and glucagon, which promote the metabolic response to stress, with hyperglycemia, water, and sodium retention, as well as increased protein and lipid intake. It is not surprising, therefore, to imagine the systemic consequences of the acute pain response, given the activation of such complex and intrinsically associated pathways[6] (Figure 1).

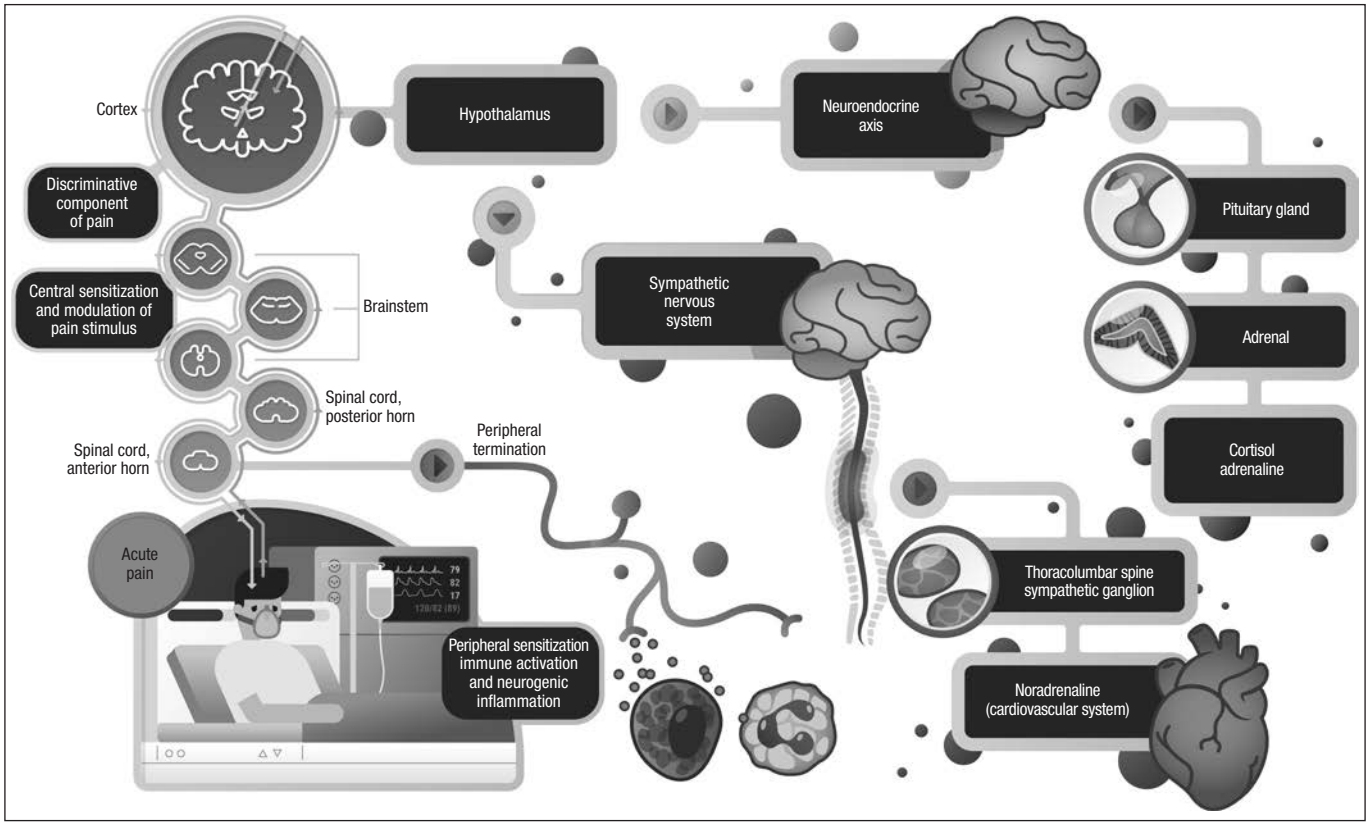

Figure 1. Pathophysiology of pain

The exact prevalence of pain in ICUs is difficult to assess, given the variability of studies, however, a systematic review indicated that approximately 50% of critically ill patients report pain and more than 35% experience severe pain at some point during their hospital stay[7]. The ICU is clearly an environment of multiple potentials for pain and, although advances have occurred in the last years, its approach is still a challenge, especially in patients that are female, on mechanical ventilation, chronically critical, young people with low resilience, psychiatric disorders (depression, anxiety, bulimia and alcohol abuse) and previous users of benzodiazepines[8,9].

In addition, the literature shows growing evidence associating poor pain control to worse clinical outcomes[10]. Poorly controlled pain in the ICU is already known to be associated with longer mechanical ventilation time, hospitalization, and *delirium*[11-13]. In a systematic review from 2015, critically ill patients evaluated for pain had outcomes related to ICU length of stay, complications, adverse events, duration of mechanical ventilation and mortality analyzed[14]. Despite methodological differences, the study confirms that systematic pain assessment seems to have a favorable impact in the short term. In the long term, it is known that patients may also develop chronic pain and post-traumatic stress syndrome[15]. If pain is responsible for these worse outcomes, on the other hand, its adequate control with epidural analgesia, for example, can reduce cardiovascular events, pulmonary thromboembolism and promote faster recovery of organic functions in selected critically ill patients[16].

Pain assessment in the intensive care unit – from known scales to new technologies

The use of pain scales in the ICU comes from a heterogeneous implementation process, with validation and training of scales in different patient profiles. Because the sensorial experience of pain is absolutely personal, the health professional's own perception is usually flawed, tending to underestimate pain, while the caregivers and/or family members of these patients tend to overestimate it[17]. A multicenter, prospective, and observational study reported that more than 50% of the analyzed ICUs had pain measurement instruments and analgesia protocols, but the application of both was less than 30% of the cohorts[18].

Although no scale alone is sensitive enough to correctly assess pain, the recommendation is that patients able to verbally report their pain must be assessed by the verbal numeric rating scale (vNRS zero – 10)[19]. The biggest challenge lies in critically ill patients with difficulties in self-expression. In the literature, it is already known that isolated fluctuations of vital signs are poor predictors of pain assessment and must be seen as an adverse event associated with severe pain[20]. In these cases, the Behavior Pain Scale[21] and the Critical-Care Pain Observational Tool (CPOT)[22] are both validated, having robust psychometric properties and similar reproducibility in published studies, both for clinical, surgical and polytraumatized patients.

It is important to consider that pain assessment in patients with traumatic brain injury, burns, patients with acute *delirium* and/or dementia is still a challenge. The studies considering this profile of patients, especially those comatose or deeply sedated, point to the use of the bispectral index and the use of pupillometry as an attempt to objectify this assessment[23]. In a study with 100 immediate postoperatory (PO) patients, a high correlation (0.88 $p<0.001$) was found between pain intensity measured by pain vNRS and the pupillary reflex measured with a bedside pupillometer as a guide for the titration of intravenous morphine[24]. Recently, the use of a new analgesia monitoring (Analgesia Nociception Index) was published, using electrocardiogram electrodes integrated with a computer model of data interpretation, including subcortical functions, bronchial receptor reflexes, the vagus nerve nucleus and the sinoatrial node stimuli[25]. Studies have been published in an attempt to validate this new modality in order to reduce opioid consumption in the PO[26]. Using similar technology, a monitor that integrates cardiac variability data with temperature, plethysmography, and skin conductance response on a multiparametric platform (Nociception Level Index), via a device placed on a chiropractor, was developed.

Through advanced artificial intelligence algorithms, nociception is presented on a scale of zero to 100, ranging from no pain to severe pain. Its validation has also been performed in perioperative patients[27] with more severe profiles. Still using artificial intelligence, a recent publication described the development of algorithms specialized in facial expression image analysis, configuring a potential tool in detection and analysis of pain and its intensity[28] at bedside in patients incapable of expressing their pain.

Pain in the intensive care unit and the (excessive) use of opioids

Opioids are the most commonly used drugs for pain management in critically ill patients, despite the current knowledge of their adverse effects, such as tolerance, dependence, and withdrawal syndrome. Tolerance seems to be an even greater problem in burn patients, patients with prolonged mechanical ventilation and pediatric patients[29]. Its use has acquired such significant dimensions that it has become a public health issue in the US. In 2017, analyzing the impact of this situation in the country's ICUs, the number of deaths due to opioid abuse has reportedly increased substantially in recent years within ICU[30].

Opioids still have formal indication for moderate to severe pain control[5], and the choice of drug and dose should be titrated according to the patient's profile. Besides inducing metabolic ileus and hypotension, the use of opioids can be related to *delirium* and immunosuppression[29,31]. In critically ill patients, particular attention should be paid to those with altered body distribution volume, polypharmacy, and renal and hepatic alterations.

The prolonged use of opioids causes persistent stimulation of neuroreceptors, promoting desensitization and signaling of pro-nociceptive pathways[29], resulting in dose escalation due to tolerance. In addition, the use of opioids in association with inflammatory states, infections and stress promotes neuroinflammation by activating glial receptors in the central nervous system[32], a factor related to the induction of hyperalgesia. According to the literature, these events seem even worse in critically ill patients when compared to other patients.

Due to this current evidence, there is an academic effort in the strategic use of analgesic measures that spare opioids. When necessary and indispensable, opioids should be used in the lowest possible doses and in a short period of time, with daily adjustments, and in association with the use of other analgesic drugs. Remifentanil, for example, should be avoided because of its potent induction of hyperalgesia. In critically ill patients with a history of opioid abuse and tolerance, rotation of opioids may be necessary to subvert desensitization of active receptors or metabolites (the use of methadone, for example). In patients with hyperalgesia, the use of opioids can cause worsening of pain, requiring the use of multimodal therapy, with activation of other nociceptive receptors for pain control[29].

Acute pain approach and multimodal therapy

The concept of analgosedation emerged in recent years, aiming at analgesia instead of sedation in acute critically ill patients, allowing minimal or no sedation, including during mechanical ventilation, with better outcomes, such as shorter ICU stay[33]. This process also promoted rationalization in the negative effects of sedatives, especially benzodiazepines.

The current broader concept of good practice is patient-centered care[34,35], allowing comfort with adequate analgesia, minimum sedation, and maximum humanization (besides open visitation policies and mobilization protocols). The logic is to customize the level of comfort (total pain)[36], trying to evaluate the pain component not in an isolated and numerical manner, but encompassing the psychosocial and affective components of patients through qualitative and functionality analysis.

Multimodal analgesia, which is characterized by pain control through the association of different drugs with several nociceptive blocking mechanisms, should be valued for being highly efficient in the treatment of pain when compared to the use of only one high-dose analgesic, besides facilitating the opioid sparing strategy, even in trauma patients[37,38]. Multimodal therapy includes the combined use of common analgesics (dipyrone and paracetamol) and controlled doses of nonsteroidal anti-inflammatory drugs (NSAIDs), besides the adjuvant use of other drugs, such as alpha-adrenergic agonists (dexmedetomidine), as well as ketamine and lidocaine, in combinations tailored to the patient's profile and analgesic needs[39,40] (Table 1).

Dexmedetomidine is a highly selective central alpha2-agonist agent with a short half-life that promotes sedative effects without central nervous system depression and has analgesic potential via modulation of the posterior horn of the spinal cord, and is currently a drug with a good titration profile in critically ill pa-

Table 1. Pharmacological options for acute pain management.

Main drugs/mechanisms of action	Indications/advantages	Adverse effects/considerations
Opioids[29]	Important role in severe acute pain	Respiratory depression, pruritus, metabolic ileus, urinary retention
G-protein-coupled opioid receptor agonists, promoting K-channel opening and inhibition of voltage-dependent calcium channels		Use should be rationalized due to adverse effects and especially to dependence and OIH
Non-steroidal anti-inflammatory drugs[40]	Good pain control, reducing inflammation	Bleeding, renal dysfunction and acute coronary syndrome
Cyclooxygenase inhibitors	Low, time-limited doses (< 48 h) are well tolerated in most patients	Multiple regimens and doses used in studies, most data against use is controversial
Gabapentinoids[40,56]	Anticonvulsants with effect on neuropathic pain or progression to chronic pain	Sedation, visual disturbances and vertigo Special care in the elderly and renal patients
Calcium channel agonist – voltage-dependent		Multiple regimens in studies involving postoperative and acute pain, with controversial data
Lidocaine[47]	Multimodal analgesic effect, with action on OIH, in low dose (± bolus) continuous infusion	Continuous infusion should be avoided for >24h Avoid in extremes of weight (< 40kg or > 120kg) Do not use intravenous dose concomitant with use or action time of other local anesthetics
Multimodal mechanism; main effect in blocking sodium channels		Risk of central nervous system and cardiovascular toxicity, especially in the presence of hepatic and renal dysfunction
Dexmedetomidine[41]	Good control of delirium/sedative effect, without respiratory depression	Hypotension and bradycardia, especially associated with dose and frail patients
Central alpha-2-agonist	Analgesic effect in perioperative studies and aid in OIH	
Ketamine[43]	Analgesic effect and in control of OIH	Dissociative symptoms, hallucinations
Blockade of N-methyl-D-aspartate receptors	Low dose continuous infusion (± bolus) can be used as adjunct in perioperative, burn and mechanic ventilation patients	Cardiovascular effects and increased intracranial pressure

OIH = opioid-induced hyperalgesia

tients[41]. Especially in surgical patients, several publications point to pain control during adjuvancy, with good tolerability (attention to hypotension and bradycardia, in particular, is required). In laparoscopic surgeries, the use of the drug reduces the intense PO pain, the need for analgesia and the time of use of rescue analgesia[42]. The literature also contains references of the adjuvant use of dexmedetomidine in the modality of patient-controlled analgesia (PCA) and as an adjunct drug in regional blockades, providing good pain control in ERAS[41] (Enhanced Recovery after Surgery) patients with opioid-free approach.

Ketamine is a drug that induces sedation and analgesia mediated by inhibition of N-methyl-D-aspartate (NMDA) receptors and activation of μ-type opioid receptors. It can cause tachycardia and hypertension, with minimal central depressant effect, but attention is required to its dissociative effects described in the literature[43]. The latest pain management consensus (2018) recommends the use of ketamine as an adjunct drug to the use of opioids for the management of PO pain in critically ill patients[5]. In addition, publications on the adjuvant use of sub-anesthetic doses (~0.1mg/kg/h) in the management of mechanical ventilation[44] and its use in the control of opioid-induced hyperalgesia[43] have been increasing. In a recent systematic review in the surgical setting, the use of ketamine was well tolerated and significantly reduced the consumption of opioids and other analgesics in general PO patients, including in orthopedic procedures[45].

Lidocaine is an antiarrhythmic drug with an anesthetic effect of multimodal mechanism, and is currently used in intravenous administration for PO pain control, in addition to its use in oncologic, OIH or neuropathic pain patients. In therapeutic concentrations, it promotes sodium channel blockade, suppression of action potentials in injured neuronal fibers, and an anti-inflammatory effect; however, at higher doses, it can promote blockade in a wide range of receptors, which can lead to high cardiovascular risk and neurotoxicity. The correlation between adequate plasma levels and signs and symptoms of toxicity does not seem to be linear[46].

As described in a recent international consensus on efficacy and safety in the use of PO analgesia, one should use up to 1.5 mg/kg/h in continuous infusion for no more than 24 h, under monitoring and reevaluation, not concomitant to the use of regional blockades[47]. The most recent systematic review, including several types of open and laparoscopic surgeries (4525 patients in 68 studies), concluded, due to the heterogeneity of the studies, that there was no significant effect on the use of lidocaine to reduce opioid consumption and pain scores in the use over 24 h[48].

In the last decades, there has been a great advance in interventional techniques for pain management. The current blockades, which are ultrasound-guided, seem safe, even in critically ill patients with coagulopathy[49]. There are benefits in analgesia, reduction of opioid consumption and chronic postoperative pain through adrenergic, inflammatory, and immune modulation, even in patients with higher morbidity and oncologic surgery patients, profiles that are very present in modern ICUs[50,51]. In orthopedic hip and knee surgeries, the role of neuroaxis anesthesia in relation to general anesthesia in reducing worse outcomes, including mortality, is well established[52].

Especially in complex thoracic and abdominal surgery patients, the use of regional blocks combined with epidural anesthesia are emphasized in the literature for better PO pain control[5,50]. Furthermore, there is the emergence of fascial planes blockades, with good evidence in acute pain management and less adverse effects (urinary retention and hypotension), especially in thoraco-abdominal approaches[53,54], favoring satisfaction, early rehabilitation, and shorter hospital stay. Despite current advances, there is still a large field of ongoing research on the topic, especially in techniques of application and management of infusions directly into more complex wounds, use of anesthetics with longer half-life (16 h x 72 h), and use of intravenous drugs and adjunct perineural to increase analgesic effects[55].

The use of opioids in PCA systems seems to be effective for pain control and improvement of patient satisfaction[57]. Modern pumps allow the drug release by the patients themselves in doses programmed by the healthcare team and with administration limits per dose and time intervals, in order to avoid build-ups and toxicity. Besides the use of opioids, the current systems allow the infusion of other analgesics (such as NSAIDs, anesthetics, and dexmedetomidine) in epidural, subcutaneous, and transdermal use[58].

Other methods of non-invasive and easy management pain control have been published, such as sublingual tablets, patches, and transdermal systems (fentanyl, lidocaine and, more recently, dexmedetomidine), but evidence is still scarce regarding their use and effectiveness in acute pain[55,58,59].

There is also a recommendation to expand the use of non-pharmacological therapies and psychotherapeutic follow-up in pain management, especially in cancer patients, such as music therapy, acupuncture, and cryotherapy[5]. The entire multiprofessional team must be familiar with these therapies, and each therapeutic proposal must be individually adapted to each patient. It is essential that reassessments be done frequently and therapies readjusted at any time, aiming at a balance between comfort and adverse effects. It is also worth noting that the increasing use of specialized pain services within the critically ill care environment seems to improve satisfaction and quality of care[60], especially in patients of more difficult management, such as those with chronic acute pain, acute pain difficult to manage after extensive trauma, patients with tolerance/dependence to opioids and in subpopulations of higher risk (elderly, sedated, severe). These (multidisciplinary) teams also assist in registries, protocol management, continued education on treatments, adverse effects encountered, and data auditing.

About the future

Translational study for promising pain control therapies in the ICU may represent a future breakthrough[61]. Among the most promising drugs, nicotinic acetylcholine receptor agonists seem to reduce glial activation, modulating the inflammatory immune response and promoting a central effect on pain and hyperalgesia mechanisms[62].

There are still issues to be explored, for example: which factors associated with gender, age, ethnicity, and behaviors affect pain perception and the pharmacogenomics of the various drugs in this context, what is the best objective measure of pain in patients who cannot communicate[63], how serum biomarkers of

pain could assist in this process[64], what are the best combinations and doses of analgesic drugs adjunct to opioids, and which other negative outcomes acute pain can cause in target organs.
Furthermore, there is a lack of randomized clinical trials on this subject, largely due to ethical issues. New studies may help in the further understanding of pain intensity assessment, efficiency of sedatives and analgesics, adverse events and complications associated with analgesics, negative outcomes, and even the association between pain and inflammation through the serum dosage of circulating neuropeptides and biochemical markers.

CONCLUSION

Because of its systemic effects and prevalence, acute pain is still a relevant problem in the ICU. New diagnostic methods are being marketed with the proposal to objectify this evaluation in complex patients. The approach to acute pain must prioritize multimodal techniques, which present more consistent clinical responses, in addition to reducing opioid consumption. The existence of multidisciplinary teams specialized in pain control in the hospital environment is able to assist in difficult cases and help in quality audits.

AUTHORS' CONTRIBUTION

Jose Mauro Vieira Junior
Conceptualization, Writing - Review and Editing
Laura Herranz Prinz
Conceptualization, Writing - Preparation of the original, Writing - Review and Editing

REFERENCES

1. Puntillo KA. Pain experiences of intensive care unit patients. Heart Lung. 1990;19(5 Pt 1):526-33.
2. Morone NE, Weiner. DK. Pain as the 5th vital sign: exposing the vital need for pain education. Clin Ther. 2013;35(11):1728-32.
3. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences and prevention. J Pain Res. 2017;10:2287-98.
4. Cohen M, Quintner J, van Rysewyk S. Reconsidering the International Association for the Study of Pain definition of pain. Pain Rep. 2018;(2):e634.
5. Devlin JW, Skrobik Y, Vice-chair F, Gélinas C, Needham DM, Slooter AJC, et al. Clinical practice guidelines for the prevention and management of pain, agitation / sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.
6. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-84.
7. Gregory J, McGowan L. An examination of the prevalence of acute pain for hospitalised adult patients: a systematic review. J Clin Nurs. 2016;25(5-6):583-98.
8. Puntillo KA, Max A, Timsit J, Vignoud L, Chanques G, Robleda G, et al. Determinants of procedural pain intensity in the intensive care unit. Am J Respir Crit Care Med. 2014;189(1):39-47.
9. Puntillo KA, Max A, Timsit JF, Ruckly S, Chanques G, Robleda G, et al. Pain distress: the negative emotion associated with procedures in ICU patients. Intensive Care Med. 2018;44(9):1493-501.
10. Olsen BF, Rustøen T, Sandvik L, Jacobsen M, Valeberg BT. Results of implementing a pain management algorithm in intensive care unit patients: the impact on pain assessment, length of stay, and duration of ventilation. J Crit Care. 2016;(36):207-11.
11. Hoc AP. Pain Assessment is associated with decreased duration of mechanical ventilation in the intensive care unit. Crit Care Med. 2009;111(6):1308-16.
12. Sebbane M, Perrigault P, Mann C. Impact of systematic evaluation of pain and agitation in an intensive care unit. 2006;34(6):1691-9.
13. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006;102(4):1267-73.
14. Georgiou E, Hadjibalassi M, Lambrinou E, Andreou P, Papathanassoglou ED. The impact of pain assessment on critically ill patients outcomes: a systematic review. Biomed Res Int. 2015:2015:503830.
15. Puntillo KA, Naidu R. Chronic pain disorders after critical illness and ICU-acquired opioid dependence. Curr Opin Crit Care. 2016;22(5):506-12.
16. Pöpping D. Impact of epidural analgesia on mortality and morbidity after surgery - systematic review and meta-analysis of randomized controlled trials. Ann Surg. 2014;259(6):1056-67.
17. Seers T, Derry S, Seers K, Moore RA. Professionals underestimate patients' pain: a comprehensive review. Pain. 2018;195(5):811-8.
18. Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, et al. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. Can J Anesth. 2014;61(7):619-30.
19. Ahlers SJ, van Gulik L, van der Veen AM, van Dongen HP, Bruins P, Belitser SV, et al. Comparison of different pain scoring systems in critically ill patients in a general ICU. Crit Care. 2008;12(1):R15.
20. Arbour C, Gélinas C. Are vital signs valid indicators for the assessment of pain in postoperative cardiac surgery ICU adults? Intensive Crit Care Nurs. 2010;26(2):83-90.
21. Payen J, Bru O, Bosson J, Lagrasta A. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258-63.
22. Fillion L, Puntillo KA, Viens C, Fortier M, City Q. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420-7.
23. Lukaszewicz A, Dereu D, Gayat E, Payen D. The relevance of pupillometry for evaluation of analgesia. Anesth Analg. 2015;120(6):1297-300.
24. Aubrun F, Beaussier M. Objective assessment of the immediate postoperative analgesia using pupillary reflex measurement. a prospective and observational study. Anesthesiology. 2012;116(5):1006-12.
25. Daccache G, Jeanne M, Fletcher D. The analgesia nociception index: tailoring opioid administration. Anesth Analg. 2017;125(1):15-7.
26. Upton HD, Hons B, Ludbrook GL, Wing A, Hons B, Hons B, et al. Intraoperative "analgesia nociception index"– guided fentanyl administration during sevoflurane anesthesia in lumbar discectomy and laminectomy: a randomized clinical trial. Anesth Analg. 2017;125(1):81-90.
27. Edry R, Recea V, Dikust Y, Sessler D. Preliminary intraoperative validation of the nociception level index. Anesthesiology. 2016;125(1):193-203.
28. Bargshady G, Zhou X, Deo RC, Soar J, Whittaker F, Wang H. Enhanced deep learning algorithm development to detect pain intensity from facial expression images. Expert Syst Appl. 2020;149.
29. Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. N Engl J Med. 2019;380(4):365-78.
30. Stevens JP, Wall MJ, Novack L, Marshall J, Hsu DJ, Howell MD. The critical care crisis of opioid overdoses in the United States. Ann Am Thorac Soc. 2017;14(12):1803-9.
31. Kosciuczuk U, Knapp P, Lotowska-Cwiklewska AM. Opioid-induced immunosuppression and carcinogenesis promotion theories create the newest trend in acute and chronic pain pharmacotherapy. Clinics. 2020;75:e1554.
32. Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR. Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol Rev. 2011;63(3):772-810.
33. Faust A, Rajan P, Sheperd LA. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. Anesth Analg. 2016;123(4):903-9.
34. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016;42(9):962-71.
35. Marra A, Ely E, Pandharipande P. The ABCDEF Bundle in Critical Care. Crit Care Clin. 2017;33(2):225-43.
36. Rustam JS, Kongsuwan W, Kitrungrote L. Comfort in patients receiving mechanical ventilation : a literature review. Crit Care Nurs J. 2018;11(2):1-7.
37. Hamrick KL, Beyer CA, Lee JA, Cocanour CS, Duby JJ. Multimodal analgesia and opioid use in critically ill trauma patients. J Am Coll Surg. 2019;228(5):769-775.e1.
38. Frauenknecht J, Kirkham KR, Albrecht E. Analgesic impact of intra-operative opioids vs opioid-free anaesthesia: a systematic review and meta-analysis. Anaesthesia. 2019;(74):651-62.
39. Wampole CR, Smith KE. Beyond opioids for pain management in adult critically ill patients. J Pharm Pract. 2019;32(3):256-70.
40. Harvin JA, Kao LS. Pain management in the surgical ICU patient. Curr Opin Crit Care. 2020;26(6):628-33.
41. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, et al. Dexmedetomidine in enhanced recovery after surgery (ERAS) protocols for postoperative pain. Curr Pain Headache Rep. 2020;24(5):21.
42. Panchgar V, Shetti AN, Sunitha HB, Dhulkhed VK, Nadkarni AV. The effectiveness of intravenous dexmedetomidine on perioperative hemodynamics, analgesic requirement, and side effects profile in patients undergoing laparoscopic surgery under general anesthesia. Anesth Essays Res. 2017;11(1):72-7.
43. Brown K, Tucker C. Ketamine for acute pain management and sedation. Crit Care Nurse. 2020;40(5):26-33.
44. Lipscomb J. Subanesthetic ketamine for acute pain in critically ill patients. US Pharm. 2020;45(4):1-10.
45. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, et al. Perioperative intravenous ketamine for acute postoperative pain in adults (Review). Cochrane Database Syst Rev. 2018;(12):CD012033.

46. Mo Y, Thomas MC, Antigua AD, Ebied AM, Karras GE Jr. Continuous lidocaine infusion as adjunctive analgesia in intensive care unit patients. J Clin Pharmacol. 2017;57(7):830-6.
47. Foo I, Macfarlane AJR, Srivastava D, Bhaskar A, Barker H, Knaggs R, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. Anaesthesia. 2021;76(2):238-50.
48. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;(6):CD009642.
49. Wiebalck A, Grau T. Ultrasound imaging techniques for regional blocks in intensive care patients. Crit Care Med. 2007;35(5 Suppl)S268-74.
50. Albrecht E, Chin KJ. Advances in regional anaesthesia and acute pain management: a narrative review. Anaesthesia. 2020;75:(Suppl 1):e101-e110.
51. Cata JP. Outcomes of regional anesthesia in cancer patients. Curr Opin Anaesthesiol. 2018;(31):593-600.
52. Perlas A, Chan VW, Beattie S. Anesthesia technique and mortality after total hip or knee arthroplasty: a retrospective. Propensity score-matched cohort study. Anesthesiology. 2016;125(4):724-31.
53. Shaker TM, Carroll JT, Chung MH, Koehler TJ, Lane BR, Wolf AM, et al. Efficacy and safety of transversus abdominis plane blocks versus thoracic epidural anesthesia in patients undergoing major abdominal oncologic resections: a prospective, randomized controlled trial. Am J Surg. 2018;215(3):498-501.
54. Sari S, Kumar J, Turan A. New peripheral nerve blocks and local anesthetics. Curr Opin Crit Care. 2021;27(6):732-42.
55. Mudumbai SC, Auyong DB, Memtsoudis SG, Mariano ER. A pragmatic approach to evaluating new techniques in regional anesthesia and acute pain medicine. Pain Manag. 2018;8(6):475-85.
56. Savard X, Pinard A, Perioperative use of gabapentinoids for the management of postoperative acute pain. Anesthesiology. 2020;133(2):265-79.
57. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 2015;(6):CD003348.
58. Morlion B, Schäfer M, Betteridge N, Kalso E, Morlion B, Schäfer M, et al. Non-invasive patient-controlled analgesia in the management of acute postoperative pain in the hospital setting. Curr Med Res Opin. 2018;34(7):1179-86.
59. Bai Y, Miller T, Tan M, Law LS, Gan TJ. Lidocaine patch for acute pain management: a meta-analysis of prospective controlled trials. Curr Med Res Opin. 2015;(31):575-81.
60. Farooq F, Khan R, Ahmed A. Assessment of patient satisfaction with acute pain management service: Monitoring quality of care in clinical setting. Indian J Anaesth. 2016;(30):248-52.
61. Knezevic NN, Yekkirala A, Yaksh TL. Basic/translational development of forthcoming opioid- and nonopioid-targeted pain therapeutics. Anesth Analg. 2017;125(5):1714-32.
62. Ren C, Tong YL, Li JC, Lu ZQ, Yao YM. The protective effect of alpha 7 nicotinic acetylcholine receptor activation on critical illness and its mechanism. Int J Biol Sci. 2017;13(1):46-56.
63. Gélinas C. Pain assessment in the critically ill adult : recent evidence and new trends. Intensive Crit Care Nurs. 2016;34:1-11.
64. Niculescu AB, Le-Niculescu H, Levey DF, Roseberry K, Soe KC, Rogers J, Jones FK, et al. Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs. Mol Psychiatry. 2019;24(24):501-22.