Acute pain management and long term outcomes

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Purpose of review
The acute inflammatory reaction induced by tissue trauma causes pain but also promotes recovery. Recovery is highly variable among peoples. Effective acute pain (AP) management is very important but remains suboptimal what could affect long term outcomes. The review questions the impact of either failure or effectiveness of AP treatments and the choice of analgesic drugs on different long-term outcomes after tissue trauma.

Recent findings
Pain control during mobilization is mandatory to reduce the risk of complications which exacerbate and prolong the inflammatory response to trauma, impairing physical recovery. Common analgesic treatments show considerable variability in effectiveness among peoples what argues for an urgent need to develop personalized AP management, that is, finding better responders to common analgesics and targeting challenging patients for more invasive procedures. Optimal multimodal analgesia to spare opioids administration remains a priority as opioids may enhance neuroinflammation, which underlies pain persistence and precipitates neurocognitive decline in frail patients. Finally, recent findings demonstrate that AP treatments which modulate nociceptive and inflammatory pain should be used with caution as drugs which inhibit inflammation like nonsteroidal antiinflammatory drugs and corticoids might interfere with natural recovery processes.

Summary
Effective and safe AP management is of far greater importance than previously realized. Evidence of suboptimal AP management in many patients and recent reports pointing out the impact of current treatments on long term outcomes argue for further research in the field.

Keywords
acute inflammation, acute pain, neurocognitive decline, personalized pain management, physical recovery, postoperative pain

INTRODUCTION

Pain is the body's alarm system. Acute pain (AP) has a protective function [1]. By its unpleasant sensory and emotional character, AP drives immediate attention and action as well as adaptive learning. AP is the principal reason for medical appointments and for up to 70% of visits to emergency departments [1]. Postoperative pain represents a common form of AP, with 50% of the patients reporting moderate to severe pain and 17% enduring unacceptable pain [2,3]. The status quo in AP management underlines the necessity to develop adapted tools to assess the effectiveness of current pain treatments [3,4].

The concept of recovery after injury has evolved from absence of mortality and morbidity to the resumption of preinjury full functioning and quality of life [5]. Recovery outcomes include disability-free survival, that is, physical and psychological recovery, disease-free survival and recently absence of dependence to drugs initially prescribed to treat acute pain (see Table 1). Pain persistence after surgery has received much attention, specifically the relationship with AP severity has been questioned [6]. Physical decline and psychological decline i.e. cognitive dysfunctions are now considered as major postoperative outcomes [7,8]. Taking into account the complexity of the pain itself and the different outcomes to consider (see Table 1), the impact of AP

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Curr Opin Anesthesiol 2023, 36:222–227

DOI:10.1097/ACO.0000000000001239

KEY POINTS

- Pain control during mobilization is mandatory to reduce the risk of complications which exacerbate and prolong the inflammatory response to trauma then, worsen acute pain and impair physical recovery.
- Acute pain treatments should be used with caution as drugs which inhibit inflammation like nonsteroidal antiinflammatory drugs and corticoids also affect the immune response and might interfere with natural recovery processes.
- Effectiveness of common analgesic treatments is variable among peoples what argues for the development of personalized management, that is, finding better responders to common analgesics and targeting challenging patients for more invasive procedures.
- Optimal multimodal analgesia to spare opioids administration remains a priority as opioids may enhance neuroinflammation and delay recovery by underlying persistent pain and precipitating neurocognitive decline in frail patients.

management on long term outcomes is far from easy to demonstrate.

Recovery after tissue trauma is highly variable among peoples. As the neurohormonal stress response and the immune response interact to promote recovery, the acute inflammatory reaction may condition patient's outcomes. Innovative research focusing on patient specific preoperative immune states has found them more predictive of postoperative recovery [9] than other previously reported risk factors like an underlying ''pain personality'' [10]. We propose here to question two aspects of AP management: How might failure or effectiveness of AP treatment affect long term outcomes? May the choice of analgesic drug have an impact on long term outcomes [11▪]?

THE BIOCHEMICAL ORIGIN OF PAIN IS INFLAMMATION AND THE INFLAMMATORY REACTION: THE IMMUNE SYSTEM–SENSORY SYSTEM RELATIONSHIP

AP is a cardinal feature of the inflammatory reaction caused by tissue injury (whatever its origin, i.e. infectious or not). Acute inflammation is a protective reaction set by the immune system in order to defend the organism, to prevent further damages and to promote tissue healing and return to body integrity [12]. Longtime considered as a passive process, the resolution of inflammation is now proved to be a highly complex active process, involving a number of immune cell types interacting in space and time [12,13]. Non resolving inflammation is the source of multiple pathologies [14]. Local or systemic persistent inflammation causes collateral organ damages and is associated to chronic pain after surgery [14]. Circulating immune cells recruited to sites of tissue injury also may infiltrate the peripheral and central nervous systems, causing neuroinflammation. In perioperative conditions, neuroinflammation has been associated to central nervous system pathologies like postoperative delirium and cognitive dysfunctions [8] and to central sensitization which participates to chronic postsurgical pain development [15].

ACUTE PAIN MANAGEMENT AND LONG TERM PHYSICAL RECOVERY

Longterm consequences of poorly relieved AP have been mainly studied in the context of surgery. Severe postoperative pain is a risk factor for lingering pain which may lead to chronic pain [16]. Chronic postsurgical pain is actually a major health issue which negatively affects the quality of life of 2–15% of patients at 3 months and later after surgery [17].

Of particular interest is the control of pain associated to mobilization which is more intense than pain at rest and more difficult to relieve. Movement evoked pain has emerged more frequently as predictor of chronic postsurgical pain than pain at rest [6]. From an evolutionary point of view, early mobilization was essential for survival [18▪]. The actual environment has changed allowing prolonged inactivity after injury without negative consequences on survival. However, reduced mobilization associated to poor pain control may negatively affect physical recovery. First, physical activity during the acute injury phase induces activation of descending pain modulatory systems, an effective mechanism for preventing pain persistence [18▪]. Second, early mobilization, cornerstone in ERAS (enhanced recovery after surgery) programs, is associated to a reduced rate of postoperative complications [19].

Recent studies have reconsidered the relationship between severe AP and persistent postoperative pain through the *mediation factor* of postoperative complications. Severe AP indeed impairs postoperative mobilization and stimulates the neurohumoral stress response with immune-related consequences. Patients who report higher postoperative pain scores present with more infectious complications at 30 days after surgery (odds ratios of 1.11 for movement evoked pain and 2.78 for unacceptable pain) [2]. Two subsequent studies have

Table 1. From tissue injury to long term outcomes

Tissue injury	Acute pain	Acute pain management issues	Long-term outcomes
Acute inflammation as protective reaction by the immune system in response to tissue damage	Body alarm system serving as temporary danger warning (protective/survival)	Various domains to be assessed and controlled to ensure the treatment effectiveness	Beyond mortality and morbidity Full recovery of preinjury global functioning and quality of life
Acute inflammation and its active resolution are complex, coordinated dynamic processes in space and time	Complex conscious multidimensional experience: **Sensory nociceptive aspects** Peripheral and central sensitization processes **Vulnerability aspects** Psychological control Gradual shift from nociceptive to emotional and limbic structures **Psycho-social aspects** Pain priming (catastrophization, major anxiety)	Pain intensity Pain acceptability (at rest, at mobilization) Pain-related physical function Pain-related self-efficacy Adverse effects, undesirable effects of treatments leading to collateral organ damages	**Disability-free survival** **Physical Recovery** Chronic pain Functional decline **Psychological Recovery** POCD PTSD Depression **Disease-free survival** Cancer recurrence Infection **Longterm medications use** Analgesics (opioids, NSAIDs) Psychotropic drugs (antidepressants, anticonvulsants)
Inflammatory response including Systemic inflammation Neuro-inflammation			
Non resolving inflammation or chronic inflammation (chronic pathological conditions) Collateral organ damages			
Preinjury Genetic background Pro-inflammatory status (disease with low grade inflammation, inflammaging)		**Preinjury** Long-lasting pain treatments	

NSAIDs, nonsteroidal antiinflammatory drugs; POCD, postoperative cognitive dysfunction; PTSD, posttraumatic stress disorder.

correlated postsurgical complications after noncardiac surgery with functionally limiting lingering pain (observational cohort study, $N = 10\ 562$ [16,20]) and possibly with 1-year chronic postsurgical pain (multicenter prospective cohort study, $N = 1313$) [21▪]. The authors have hypothesized that major medical complications by exacerbating and prolonging the inflammatory postsurgical response may have both worsen AP and promoted pain chronification. Functional recovery, that is, mobility, self-care and ability to conduct usual activities, is an important patient-centered outcome. Two recent studies, after cardiac surgery [22] and noncardiac surgery [7] report functional decline in 22–25% of patients at 1 year postsurgery. Here, also the presence of postoperative inflammatory or infectious complications has been incriminated.

The high incidence of severe pain questions the effectiveness of current multimodal AP treatments, evidence-based and procedure-specific treatments, used in the majority of patients [23]. Understanding why some patients fail to respond to standard treatment should help to improve healthcare [24]. Failure of postoperative treatments to provide acceptable pain intensity might serve as a risk factor for poor outcome. In a 2006 editorial, Eisenach already suggested that celecoxib treatment failure might be indicative of high risk for chronic pain at donor site after spine fusion surgery [25]. Inadequate multimodal analgesia in patients reporting severe AP and then developing chronic postsurgical pain after knee replacement has also been questioned [26]. Nonsteroidal antiinflammatory drugs (NSAIDs) are considered as ''basic analgesics'' in

multimodal analgesic regimen [23]. However, a considerable interindividual variability exists in their analgesic efficacy [27]. First, heterogeneity in the activation of the inflammatory prostanoid system in response to surgical trauma might explain the phenomenon as less pronounced activation was associated with insufficient pain relief after ibuprofen administration [27]. Second, the variability in endogenous pain modulatory systems functioning also participates to the response to NSAIDs as demonstrated in patients with osteoarthritis [28]. Finally, preoperative pro-inflammatory status might affect analgesics effectiveness as patients with inflammatory background got better pain relief from ketorolac than tramadol after inguinal hernia repair [29]. Effective basal analgesic drugs in multimodal analgesia may yield greater opioid sparing effect and perhaps better pain outcome. Opioids are potent analgesics but high doses and repeated administration induces neuroinflammation which in turn exacerbates and maintain postinjury pain according to experimental animal models [30,31].

Common baseline analgesics like NSAIDs damp the inflammation but also affect the immune response with potential long term consequences [11▪]. Therefore, treatments which modulate nociceptive and inflammatory pain should be used with caution, in a temporarily and highly controlled fashion. Whether perioperative NSAIDs and corticoids do not prevent the development of chronic postsurgical pain [32], their use in a different context i.e. low back pain rises new concern [33▪▪]. A recent study has identified the protective effect of acute inflammatory responses mediated by neutrophils activation against the development of chronic musculoskeletal pain. In a preclinical rodent model, impairing the inflammatory response with NSAIDs or dexamethasone use (but not other analgesics), besides a temporary analgesic effect, prolonged the resolution of painful behavior [33▪▪]. Using a large UK Biobank, the authors supported their preclinical findings, that is, drugs which inhibit inflammation might interfere with natural recovery processes. Individuals with acute back pain taking NSAIDs are at 1.76-fold of developing chronic back pain compared with those not taking NSAIDs. Although the study suffers some limitations, these findings deserve the attention as they have been controlled for several confounding factors.

By contrast to the negative effect of poor pain relief, could improve AP management yield better physiological outcome in some patients? Pain trajectories are predominantly defined by patient factors and 63% of patients are in the moderate-to-high pain trajectories [34]. Challenging patients, that is, ''high pain responders'' include those with exaggerated stress response, both neuroendocrine and inflammatory, pain catastrophizers, patients receiving longterm high doses of opioids [5,24]. In breast cancer surgery, addition of parietal block to multimodal analgesic regimen was associated both to better AP control and to reduced chronic pain severity at 12 months in women with high baseline catastrophizing scores [35]. In the women with no/low baseline catastrophizing, addition of parietal block had less benefit, no significant impact on postoperative AP and chronic pain severity. High catastrophizers show enhanced activity in cortical regions involved in the affective processing of pain and reduced activation of endogenous pain-inhibitory systems. Regional analgesia may help to prevent the manifestations of these mechanisms, particularly the preactivation (priming) of pain-related area into the brain [35]. Trauma often causes intense AP and high stress state which may induce persistent pain [36] and posttraumatic stress disorders (PTSD) [37]. The benefits of early pain management have been highlighted in military personnel who suffered combat-related injury. In a recent prospective cohort study ($N = 358$), regional analgesia within the first 7 days after injury improved pain intensity (including neuropathic pain intensity) up to 12 months after trauma [38]. An older study ($N = 696$) also demonstrated that morphine administration during trauma care reduced the risk of subsequent PTSD (odd ratio 0.47) by preventing memory consolidation [39].

ACUTE PAIN MANAGEMENT AND LONG-TERM PSYCHOLOGICAL RECOVERY

Neurocognitive recovery is a major point of interest. Postoperative cognitive dysfunctions (POCD) complicate the recovery of elderly patients. Their incidence may reach 10–17% at 3 months and around 3% at 1 year after surgery [40]. POCD are associated to decrease quality of life, persistent neurocognitive disorders and increased mortality and morbidity. Though postoperative delirium, an acute fluctuating cognitive dysfunction, has been statistically correlated with long-term POCD in multiple studies, no direct causal link between those entities has been demonstrated [40]. The mechanisms underlying POCD are not fully understood but oxidative stress and neuroinflammation seem to play a key role [8,40]. Tissues injuries lead to the release of pro-inflammatory cytokines which affect the blood-brain barrier permeability and induce a state of neuroinflammation. Several studies have pointed out changes induced by surgery in human plasma and also cerebrospinal fluid proteome up to 30 days after tissue trauma, the majority being linked to the

pro-inflammatory interleukin 6 (IL-6) pathway [41]. In turn, neuroinflammation causes neuronal damages in more susceptible brain areas like hippocampus that is of critical importance in memory circuit [40]. Some individuals are particularly vulnerable to POCD like older patients already presenting with mild cognitive impairment characterized by subclinical unnoticed cognitive decline [42]. Further, in elderly peoples, the presence of ''inflammaging'' turns the immune system into a pro-inflammatory state unable to respond adequately to stress states [43].

Effective AP management is important, particularly in vulnerable patients to reduce the risk of complications, which may aggravate the postoperative inflammatory reaction, a risk factor of persistent pain as previously discussed. In contrast with results found in preclinical studies regarding POCD preventive strategies, human studies are mainly inconclusive due to populations heterogeneity and the variability in the cognitive tests used [40]. Paracetamol, an analgesic drug also possesses antioxidative properties. Despite a reduction in delirium incidence, no correlation between paracetamol administration and cognitive impairment at 1 and 12 months after cardiac surgery could be demonstrated [44]. Among antiinflammatory drugs, COX-2 inhibitors are often used in elderly patients. A recent meta-analysis (8 randomized controlled trials [RCTs], $N = 1106$) suggested that parecoxib might be effective in reducing POCD after orthopedic surgeries [45]. However, the results must be interpreted cautiously due to possible underpowering of the RCTs included [11▪]. The potent anti-inflammatory corticoid dexamethasone does not reduce POCD after cardiac surgery (13.6% versus 7.2% in the placebo group, $P > 0.05$) [46]. These results point out the failure of short term, isolated interventions to prevent POCD occurrence. Interestingly, ERAS programs based on a multidisciplinary, multimodal approach designed to control the surgical stress response and the inflammatory response to hasten recovery [5] may be more effective to reduce POCD [47▪]. In fast track hip and knee arthroplasties, the incidence of POCD at 3 months is low, that is, 8–9% [47▪]. In a subanalysis investigating the role of perioperative factors, patients with POCD consumed higher doses of postoperative opioids in both the acute period and the 2–3 weeks after discharge [48]. These findings once again support the benefits of opioid sparing analgesic strategies in the perioperative period. In experimental conditions, opioids induce neuroinflammation. An interesting experimental study in aged rats demonstrated that combination of aging plus surgery plus morphine treatment provokes prolonged memory alteration that mimics POCD. The morphine contribution to this cognitive impairment phenomenon seems to be independent of μ-receptor but linked to Toll-like receptor-4 pathway and requires an initial neuroinflammation background [49].

CONCLUSION

Effective AP management is of far greater importance than previously realized but remains suboptimal what could affect long term outcomes. Common analgesic treatments damp the inflammatory reaction caused by tissue trauma and affect the immune response with potential consequences. Recent findings demonstrate that AP treatments should be used with caution as drugs which inhibit inflammation like NSAIDs and corticoids might interfere with natural recovery processes. Further, analgesic treatments show considerable effectiveness variability among peoples what argues for the development of personalized AP management, that is, finding better responders to common analgesics and targeting challenging patients for more invasive procedures. Optimal multimodal analgesia to spare opioids administration remains a priority as opioids may enhance neuroinflammation and delay recovery by underlying persistent pain and precipitating neurocognitive decline in frail patients.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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