Preventive analgesia

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Purpose of review

This paper will discuss the concepts of pre-emptive and preventive analgesia in acute and persistent postsurgical pain, based on the most recent experimental and clinical literature, with a special focus on injury-induced central sensitization and the development from acute to chronic pain.

Recent findings

The nature of central sensitization during acute and chronic postsurgical pain share common features, and there may be interactions between acute and persistent postoperative pain. The term 'pre-emptive analgesia' should be abandoned and replaced by the term 'preventive analgesia'. Recent studies of preventive analgesia for persistent postoperative pain are promising. However, clinicians must be aware of the demands for improved design of their clinical studies in order to get more conclusive answers regarding the different avenues for intervention.

Summary

The concept of preventive analgesia is still an attractive working hypothesis but with inconclusive results. A plea for better design of clinical studies is forwarded.

Keywords

analgesia, central sensitization, pain, pre-emptive analgesia, preventive analgesia

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Introduction

Acute postoperative pain is a result of noxious stimulation of skin, subcutaneous tissues, as well as of neural and visceral structures involved in the surgical procedure. Nociceptive pain is augmented by inflammatory pain due to inflammatory mediators released at the wound site, which creates a reduction in the threshold of local nerve endings (peripheral sensitization), and by neuropathic components as damage to neural tissue is inevitable in most surgical procedures [1].

Owing to the afferent barrage of impulses from the injury, central neurons become hyperexcitable, leading to an exaggerated response by these neurons to normal sensory inputs (central sensitization). Early experimental observations demonstrated that analgesics applied before injury were more effective in reducing central sensitization as compared with administration after injury [2•].

The idea of pre-emptive analgesia of acute, postoperative pain was based on these initial experimental observations. It was hypothesized that it may be advantageous to prevent the noxious input from gaining access to the central nervous system (CNS) and, thus, to preempt rather than to treat pain, when the consequences of such inputs are already established [3].

In recent years, there has been an increased focus on chronic or persistent pain after surgery, as it has been estimated that acute postoperative pain is followed by persistent pain in 10–50% of individuals, and that it may be severe in about 2–10% of these patients [1]. Consequently, persistent postoperative pain represents a major clinical problem.

The pathophysiology of persistent postoperative pain most probably includes either ongoing inflammation or a manifestation of neuropathic pain [1]. It has been hypothesized, however, that severe, unrelieved acute postoperative pain *per se* may result in an increased incidence of persistent postoperative pain [1,2•]. Consequently, it has been speculated, whether aggressive perioperative, 'preventive' analgesia, including antihyperalgesics, nerve blocks, and multimodal analgesia may reduce the development of persistent postoperative pain [1,2•].

In this paper, we will discuss the concepts of pre-emptive and preventive analgesia in acute and persistent postsurgical pain, based on the most recent experimental and

clinical literature, with a special focus on injury-induced central sensitization and the development from acute to chronic pain.

Central sensitization in acute postoperative pain

As emphasized above, acute postoperative pain is driven by nociceptive inputs that are amplified by sensitized peripheral and central neurons. The mechanisms and clinical role of central sensitization in various pain states have been reviewed recently [2•,4••]. Central sensitization is due to increases in membrane excitability, synaptic efficacy, and reduced inhibition in somatosensory and nociceptive pathways, in response to nociception, inflammation, and neural injury [4••].

The molecular mechanisms involved are complex and include an early, nociceptor-driven response. This results mainly from rapid changes in glutamate receptor and ion channel properties, and is usually relatively short-lasting and reversible. This activity-dependent sensitization has been characterized as an adaptive or protective mechanism serving to reduce ambulation and promote healing [4••]. In this state, pain is elicited by innocuous stimuli, and sensitization may be maintained by a low level of afferent input. Such first-line sensitization is most probably the phenomenon in play in 'normal' acute postoperative pain. The clinical consequences are spontaneous pain and increased sensitivity in tissues adjacent to the wound, leading to unprovoked pain at rest and intensified pain during movement [4••].

Central sensitization in chronic postoperative pain

Ongoing pain due to peripheral inflammation and nerve injury may lead to a later and longer-lasting, sometimes persistent phase of central sensitization. The first-line and second-phase central sensitization share molecular and cellular mechanisms, including changes in glutamate receptors and ion channels [4••]. Some mechanisms are, however, unique to the second-phase central sensitization induced by either inflammation or nerve injury. These include spontaneous peripheral ectopic generation of action potentials, structural changes such as altered synaptic function, sprouting of central neurons, and apoptosis of inhibitory interneurons resulting from N-methyl-D-aspartate receptor (NMDAR)-induced excitotoxicity, and activation of microglia that produce and release trophic factors, neurotransmitters, and cytokines [4••]. Inflammatory and in particular neuropathic-induced second-phase central sensitization is clinically characterized by being un-coupled to noxious stimulation, resulting in spontaneous pain, allodynia, hyperalgesia, and after-sensations [4••].

Key points

- 'Pre-emptive' analgesia defined as a treatment that is initiated before in contrast to after the surgical procedure.
- 'Preventive' analgesia is based on the assumption that the only way to prevent central sensitization might be to completely block any pain signals from the surgical wound from the time of incision until final wound healing.
- Preventive analgesia is an attractive working hypothesis, but the data are inconclusive regarding effects on persistent postsurgical pain. This may not be explained by a wrong hypothesis but rather that most of the available studies have had problems in design to answer the right questions.

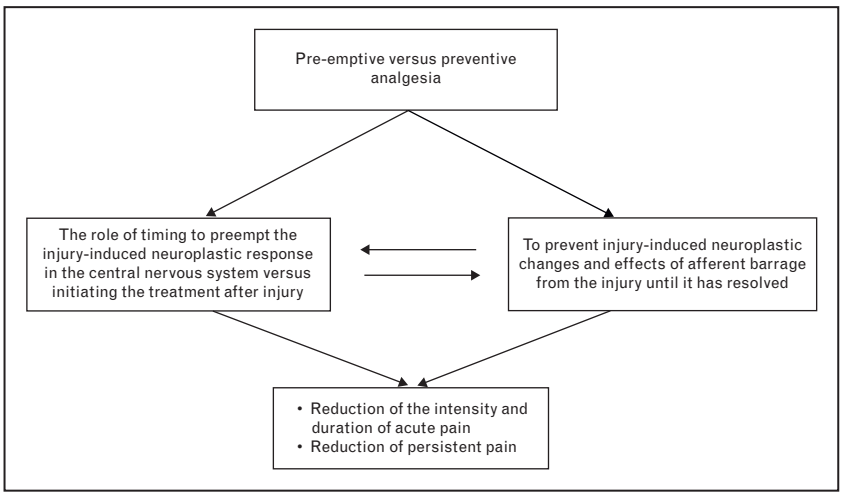
In summary, the nature of central sensitization during acute and chronic postsurgical pain share common features, and there may be interactions between acute and persistent postoperative pain (Fig. 1). However, some mechanisms are unique to either inflammation or nerve injury and it is also important to realize that neuropathy is not necessarily equivalent to persistent pain [5,6]. These observations may have impact on the ability to preempt acute, and in particular, to prevent persistent postsurgical pain.

Transition from acute to persistent postoperative pain: definitions and predictive factors

The definition by the International Association for the Study of Pain (IASP) of chronic postoperative pain as 'a persistent pain state that is apparent more than 2 months postoperatively, and which cannot be explained by other causes' has been disputed to be too simplistic [7]. It has been argued that most of the literature that has followed this definition 'is composed of reports with insufficient pain assessment and little information regarding its consequences' [7]. Thus, it is important for future studies to include a detailed assessment of the location, characteristics, and evolution of painful symptoms, to document changes in neurologic function as well as to assess the consequences of persistent pain on physical and social function (Table 1) [7].

So far, the mechanisms underlying transition from acute to persistent postsurgical pain are only about to be uncovered [1,8,9]. In addition to ongoing inflammation, neuropathy, and unrelieved pain, a number of other risk factors have been suggested. These include preoperative pain, psychosocial factors such as depression, psychological vulnerability, stress, preoperative anxiety and catastrophizing, sex, type of surgery, recurrence of malignancy, adjuvant therapy, and genetic susceptibility [1,8,9]. It is unclear whether the relationship between acute and persistent postoperative pain is causal, is due to

Figure 1 Pre-emptive versus preventive analgesia



'Pre-emptive' analgesia is a treatment that is initiated before in contrast to after the surgical procedure. 'Preventive' analgesia is based on the assumption that the only way to prevent central sensitization might be to completely block any pain and afferent signals from the surgical wound from the time of incision until final wound healing.

extensive neuroplastic changes, insufficient perioperative analgesia, or if it may be a consequence of common preoperative predisposing factors [9,10]. Uncovering of potential risk and predictive factors for persistent postoperative pain may help to establish rational recommendations for prevention and therapy [10,11•,12].

'Pre-emptive' and 'preventive' analgesia: definitions

'Pre-emptive' analgesia is most often defined as a treatment that is initiated before in contrast to after the surgical procedure. Consequently, it is operational during surgery in order to reduce the physiological consequences of afferent nociceptive transmission provoked by the procedure. With this definition, timing of analgesia is crucial. 'Preventive' analgesia is based on the assumption that the only way to prevent central sensitization might be to completely block any pain and afferent signals from the surgical wound from the time of incision until final wound healing. In contrast to timing, this concept is focused on the intensity and duration of the analgesic intervention [13].

Pre-emptive analgesia for acute surgical pain: clinical evidence

The interpretation of clinical findings from randomized, controlled trials of pre-emptive analgesia in acute postoperative pain is debatable [13,14]. Some studies have found significant effects, whereas in the majority, no differences between preoperative and postoperative administration of various drugs have been demonstrated. Thus, it is the general interpretation that no major or consistent clinical benefits have been revealed [15,16]. In a recent meta-analysis investigating the effect of pre-emptive incisional or intraperitoneal local anesthetic [17], intraperitoneal local anesthetic administered before surgery reduced postoperative pain compared with postoperative administration, but this reduction was small and clinically insignificant [17]. No effect of pre-emptive incisional local anesthetic was demonstrated [17].

It should be emphasized that the overall negative observations with pre-emptive analgesia should not serve to disprove central sensitization as an important mechanism in acute, postoperative pain. Rather, the negative results

Table 1 Elements of the study design of preventive analgesia

Preoperatively	Intraoperatively	Early postoperatively	Late postoperatively
Presence of pre-existing pain (locally and remote)	Descriptive characteristics about the incision	Pain intensity, character, and functional consequences	Pain intensity, character, and functional consequences
Measurement of the functional consequences of pre-existing pain	Descriptive characteristics about handling of nerves and muscles	Pain treatment modality used	Psychosocial consequences
Neurophysiologic assessment	Information about the disease being treated	Neurophysiologic assessment	Neurophysiologic assessment
Psychosocial assessment			
Analysis of 'pain genes'			

Adapted with permission from [7].

Table 2 Recent examples of randomized, placebo-controlled double-blinded trials examining preventive analgesia

Reference	Preventive treatment	No. in active/ placebo groups	Surgical procedure	Primary outcome	Information about preoperative status (pre-existing pain, neurophysiology, psychosocial)	Information about intraoperative characteristics (incision, handling of nerves)	Information about early postoperative pain (intensity, character, treatment, neurophysiology)	Information about late postoperative pain (intensity, character, treatment, neurophysiology)	Outcome, late postoperative pain	Comment
Remerand *et al.* [18]	i.v. ketamine 0.5 mg/kg before incision, followed by 24-h infusion with 2 μg/kg/min)	79/75	Total hip arthroplasty	Morphine consumption during the first 24 postoperative hours	Preoperative pain location and rating (at rest and while walking), need for help with walking, and analgesic consumption was noted. Patients receiving chronic treatment with gabapentin, clonazepam, strong opioids were not included	Type of prosthesis, cement use	Morphine consumption 0-24 h and 0-7 days postoperatively significantly reduced in ketamine group. Pain scores at rest, getting out of bed, during the first steps, and worst pain scores from day 0 to day 7 were similar in both groups	Patients were interviewed by phone on days 30, 90, and 180 for pain location and intensity (at rest and while walking), need for help when walking, and analgesic consumption	At day 180, 21% of placebo group patients (15 of 70) experienced pain at rest in the operated hip versus 8% (6 of 72) in the ketamine group ($P=0.036$). Ten versus three patients in the placebo versus the ketamine group with persistent pain rated their pain at rest higher than 3 ($P=0.04$)	Assessment of late postoperative pain by phone. Primary out come acute post operative pain
Sen *et al.* [19]	Gabapentin 1200 mg before surgery	30/29	Inguinal herniorrhaphy	Level of chronic pain, time point not specified	Patients with presence of psychiatric problems were not included	All operations were performed by the same surgeon with the same technique (Lichtenstein)	Total tramadol consumption at 8-24 h postoperatively reduced in gabapentin group ($P<0.05$). VAS scores (lying and sitting position) 8-24 h after surgery reduced in gabapentin group ($P<0.05$)	Patients were interviewed by phone at 1, 3 and 6 months with an 11-point numerical rating scale	NRS scores at 1, 3, and 6 months after surgery were reduced in the gabapentin group ($P<0.05$)	Assessment of late postoperative pain by phone. Only one dose of preoperative gabapentin. Small study groups. Primary outcome not clearly specified
Sen *et al.* [20]	A: i.v. ketamine 0.3 mg/kg before incision, followed by infusion with 0.05 mg/kg/h until the end of surgery B: Gabapentin 1200 mg before surgery	20/20/20	Abdominal hysterectomy	Level of pain, type and time point not specified	Patients with presence of chronic pain syndrome, psychiatric problems, previous prescription of gabapentin and analgesic treatment (opiates, tricyclic antidepressants or venlafaxine, pregabalin, clonazepam, carbamazepine, and NMDAR blockers) were not included	The operation was performed via a Pfannenstiel incision by the same surgeon	Total PCA morphine use significantly decreased in the ketamine and gabapentin groups, respectively, compared with the control group. VRS pain scores while lying and sitting were significantly lower in the gabapentin group compared with the control group at all measurements for 24 h, and in the ketamine group for all measurements in the first 16 h postop.	Patients were contacted at 1, 3, and 6 months after discharge to inquire whether they had any residual postoperative (incisional) pain (VRS)	At the 1-month, 3-month, and 6-month follow-up, both the incidence of incisional pain and pain scores were reduced in the gaba pentin group com pared with the ketamine and control groups ($P=0.001$)	Assessment of late postoperative pain by phone (?). Small study groups. Primary outcome not clearly specified
Duale *et al.* [21]	i.v. racemic ketamine 1.0 mg/kg before incision, followed by infusion with 1 mg/kg/h during surgery, and 1 mg/kg for 24 h postoperatively	39/41	Thoracotomy	Level of chronic pain at the 6th week after surgery	Patients with previous thoracic chronic pain, previous neuropathic pain (whatever the site), analgesic treatment (opiates, tricyclic antidepressants or venlafaxin, gabapentin or pregabalin, clonazepam, carbamazepine, NMDAR blockers), advanced phase of cancer were not included	No information	Total PCA-morphine use not statistically different between groups during 24 h postoperatively Global intensity of pain and the number of observations in which VAS > 3/10 was reduced in ketamine group during 24 h postoperatively	Clinical signs (hypoesthesia, hyperalgesia, allodynia (von Frey hair and brush), and size of the pathological areas were determined 6 weeks and 4 months after surgery Patients recorded symptoms in personal booklet; Neuropathic Pain Symptom Inventory (NPSI); Health-Related Quality of Life questionnaire SF-36	No difference in any outcome	

Dullenkopf *et al.* [22]	i.v. ketamine 0.15 mg/kg, or 0.5 mg/kg (single dose before incision)	36/41/33	General and orthopedic surgery	Morphine consumption during the first 24 h after surgery	Patients in actual therapy with psychoactive drugs or opiates, history of severe psychological disturbances were not included	No information	Total nurse-administered morphine use after 24 h, or rating of pain therapy after 48 h not statistically different between groups during 24 h postoperatively	Three months after surgery, all patients were contacted by mail and were asked to quantify persisting pain related to the site of the operation	No difference in any outcome	Assessment of late postoperative pain by mail. Only one dose of preoperative ketamine. Primary outcome acute postoperative pain
Buvanendran *et al.* [23••]	Pregabalin 300 mg orally 1–2 h before surgery, 150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on days 11 and 12, and 50 mg twice daily on days 13 and 14	113/115	Knee arthroplasty	Incidence of neuropathic pain at 6 months postoperatively	Patients with prior use of gabapentin (or pregabalin) or NSAIDs within 2 weeks before surgery; with a history of neuropathic pain or any other chronic pain condition, were not included	Surgical procedure thoroughly described	In the immediate post operative period, epidural drug consumption was significantly less in the pregabalin group. Supplemental postoperative oral opioid use over the entire hospital stay was significantly less in the pregabalin group. NRS values at rest, during the immediate postoperative phase, did not differ between treatment groups	Telephone interview at 3 and 6 months. Patients with a Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) score of 12 or more at 6 months came for a standardized physical examination, including assessment of allodynia and hyperalgesia. Analgesic consumption was monitored	At 6 months postoperatively, the incidence of neuropathic pain was 0% (0 of 113) in the pregabalin group and 5.2% (6 of 115) in the placebo group ($P = 0.014$). The incidence of allodynia and hyperalgesia in the operated leg was also lower at 6 months for the pregabalin group	
Burke and Shorten [24]	Pregabalin 300 mg at 90 min preoperatively and 150 mg at 12 and 24 h postoperatively	18/20	Lumbar discectomy	Improvement in VAS score from preoperatively to 3 months postoperatively between study groups	Patients with chronic lumbar sacral radiculopathy were included. Patients with LBP of <3- month or >12-month duration, previous lumbar surgery, previous treatment with pregabalin or gabapentin, neurological or psychiatric disorders, or spinal structural abnormalities were not included. Preoperatively all patients completed six questionnaires (pre-existing pain, psychosocial). A transcutaneous electrical stimulus was used to assess threshold preoperatively	No information	VAS pain scores similar in the two groups at 24 h postoperatively. Number of patients who received supplementary analgesia within 24 h of discharge from PACU less in pregabalin-group	At 3 months postoperatively, patients completed the same six questionnaires. Each patient's impression of outcome was recorded, on a 4-point Likert scale as were any self-administered analgesic medications. A transcutaneous electrical stimulus was used to reassess thresholds postoperatively	The VAS pain decrease was greater in patients who received pregabalin. The Roland Morris Disability Question naire score, the SF-36-physical function, and the Medical Outcomes Study SF-36 total physical component-score, were improved in the pregabalin compared with the placebo group	Included patients suffered from chronic pain. Small study groups
Ryu *et al.* [25]	100 mg of S(+)-ketamine was added to an epidural patient-con-trolled regimen, which was continued until the third postoperative day	65/68	Thoracotomy	Presence of any pain around the incision site 3 months after the thoracotomy	Patients with a history of previous thoracic surgery, chronic pain, psychiatric disease, or neurologic deficits, were not included	A classic posterolateral thoracotomy incision at the T5-6 intercostal space was performed. One surgeon performed all the surgical procedures	No information	VAS pain scores during rest and coughing were assessed at 2 weeks and at 3 months after surgery at the outpatient clinic by a blinded surgeon. The presence of allodynia and numbness at the scar was assessed at 3 months after surgery	No difference in any outcome	No informa-tion about acute postoperative pain/an-algesic requirements

(*Continued next page*)

Table 2 (*continued*)

Reference	Preventive treatment	No. in active/ placebo groups	Surgical procedure	Primary outcome	Information about preoperative status (pre-existing pain, neurophysiology, psychosocial)	Information about intraoperative characteristics (incision, handling of nerves)	Information about early postoperative pain (intensity, character, treatment, neurophysiology)	Information about late postoperative pain (intensity, character, treatment, neurophysiology)	Outcome, late postoperative pain	Comment
Kim *et al.* [26]	Pregabalin 150 mg 1 h before surgery, with the dose repeated after 12 h	47/47	Endoscopic thyroidectomy	Pain during the early postoperative period	Patients with a history of seizure disorder, in current therapy with pregabalin, gabapentin, or any opioid, any physical or psychiatric condition that could impair their ability to cooperate with postoperative data collection were not included	Thyroidectomy was performed using the axillary approach with the aid of the da Vinci Robot System	Median VNRS score was significantly lower in the pregabalin group at 6, 24, and 48 h postoperatively. The number of patients who needed additional analgesics was significantly smaller in the pregabalin group during the first 1–24 h postoperatively	The incidences of chronic pain and hypoesthesia of the anterior chest were recorded at 3 months after surgery (method not specified)	No difference in any outcome	Method of late post operative pain assessment not clearly specified. Primary outcome acute postoperative pain
Amr and Yousef [27]	A: Venlafaxine 37.5 mg/day, for 10 days starting the night before operation; B: gabapentin 300 mg/day, for 10 days starting the night before operation	50/50/50	Partial or radical mastectomy with axillary dissection	Need for 24 h immediate postoperative opioid requirements	Patients taking antidepressant, anticonvulsant medications, or opioids, or with neuropathic disease were not included	Not specified. Number of patients receiving chemotherapy and/or radiotherapy noted	VAS scores after movement were significantly reduced in the gabapentin group from day 2–10, and in the venlafaxine group from day 8–10. Total morphine consumption in the ward in the first 24 h was significantly reduced in gabapentin group. Codeine and paracetamol consumption given orally from day 2–10 were significantly reduced in the venlafaxine and gabapentin groups compared to the control group	Pain scores (VAS) were recorded at rest and movement at 6 months postoperatively. Movement consisted of abduction of the arm on the operated side by 90 degrees. Patients were invited to a pain evaluation 6 months later. In addition, they were requested to complete a short questionnaire	Pain scores with movement at 6 months were significantly higher in the control and gabapentin groups compared with the venlafaxine group. The incidence of burning pain was significantly decreased in the venalafaxine group in com-parison with the control group. Stabbing or pricking was significantly reduced in the venlafaxine group in comparison with the control and gaba-pentin groups	Primary outcome acute postoperative pain. Surgical procedure (partial or radical mastectomy with or without axillary dis section) not clearly specified

i.v., intravenous; NRS, numeric rating scale; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia; VNRS, verbal numeric rating scale; VRS, verbal rating scale.

may be due to induction of central sensitization from the wound site when the initial effect of the short-term preemptive analgesic has disappeared, or to insufficient nociceptive blockade during surgery [13,15]. Thus, administration of prolonged, aggressive, and multimodal analgesia, including antihyperalgesic drugs, outlasting nociceptive activity from the wound, seems necessary to provide sustained and effective postoperative analgesia [13,15].

Prevention of persistent postoperative pain

As mentioned previously, it has been hypothesized that severe, unrelieved acute postoperative pain may be causally related to persistent postoperative pain and that perioperative, 'preventive' analgesia, including antihyperalgesics may reduce the development of persistent postoperative pain [13,15]. Some earlier studies have claimed a beneficial effect of various perioperative analgesics on late postoperative pain, but the methodology of most of these studies has been questioned [15].

Recently, a number of studies have focused on the potential beneficial effect of various antihyperalgesic drugs such as ketamine and the gabapentinoids on persistent postoperative pain [18–27] (Table 2). Several of these studies have shown promising results, that is, reduced pain 3–6 months postoperatively [18–20,23••, 24,27]. Unfortunately, the methodology of many of these studies is not sufficient to allow final conclusions. Thus, in a number of the positive studies, late postoperative pain was assessed by telephone [18–20], study groups were small [20,24], the analgesic intervention was short-term (< 24 h) [18–20,24], or the surgical procedure not specified [27]. Consequently, it is difficult to make any firm conclusions as to a potential favorable effect of these measures on the development of persistent postoperative pain.

Future strategies

Experience from the last decade has shown that the term 'pre-emptive analgesia' should be abandoned and instead replaced by the term 'preventive analgesia' [16]. Also, it is clear that this topic is still an attractive working hypothesis, although the data are inconclusive regarding effects on persistent postsurgical pain. This may not be explained by a wrong hypothesis but rather as shown in Table 2 that most of the available studies have had problems in design to answer the right questions [7,28]. What then can we demand and expect from future studies? First of all, it will be required to include all risk factors for development of high intensity acute as well as persistent postsurgical pain [7]. Such studies should include detailed assessment of the preoperative pain sensitivity [7,12], surgical handling of nerves, and of functional consequences of pain on a procedure-specific basis. Furthermore, we should expand our analgesic armamentarium from conventional NSAIDs, opioids and other nonopioid analgesics, including regional analgesic techniques to include interventions into more central pain mechanisms, including modification of the microglia response. In this context, the future may be bright and calling for studies of several drugs such as blocking nerve growth factor [29], modulating microglia activation by propentofylline [30] or minocycline [30,31], use of transient receptor potential cation channel, subfamily V, member 1 (TRPV1) antagonists [32] or various cytokine antagonists with a focus on interleukin-1β (IL-1β) [33], IL-6 antagonists [34], or cannabinoid receptor antagonists [35]. In this context, we should not be naive and repeat previous history of short-term analgesic interventions, as optimal preventive treatment most probably will require a prolonged intervention until the peripheral inflammatory response and afferent input has resolved.

Conclusion

The hypothesis of the concept of preventive analgesia is still alive and hopefully with a bright future. However, clinicians must be aware of the demands for improved design of their theory of clinical studies in order to get more conclusive answers regarding the different avenues for intervention, compared to previous efforts.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 359).

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