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REVIEW

Peri-operative pain and its consequences

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Summary Recent advances in the management of peri-operative pain principally concern the recognition of the risk of developing pain chronicity. The best identified risk factors for pain chronicity are the presence of pain pre-operatively, pre-operative opioid use, and the intensity of post-operative pain. Ideal management of peri-operative pain in 2015 aims to optimize post-operative pain management, to detect the risk of pain chronicity begins pre-operatively with early detection of risk factors for chronicity. In terms of treatment, the systematic and generous use of morphine has shown its limitations, particularly due to reduced efficacy for movement-related pain. Meanwhile, opioid side effects can be very debilitating for the patient, leading to delay in post-operative rehabilitation, a dose-dependent hyperalgesic effect resulting in both acute and chronic pain, immune modulation that may have a deleterious impact on infectious complications or cancer [1], and, finally, some question of possible neurotoxicity. Therefore, modern analgesia depends on both intra-operative and post-operative morphine sparing. The goal at the present time is to obtain optimal analgesia that allows rapid rehabilitation without sequelae or chronicity through the use of drugs and/or techniques to avoid the need for opioid medications.

Beyond obvious ethical considerations, the management of peri-operative pain is fundamental in order to limit the consequences of post-operative pain. Poorly controlled pain has physiological and psychological consequences that are associated with morbidity in terms of complications, delayed wound healing, and prolonged hospitalization and risk of chronic pain. Today, it has been fairly well demonstrated that the intensity of post-operative pain is a predictor of chronic post surgical pain (CPSP) [2]. There is a continuum between poorly treated acute post-operative pain and evolution to chronic pain.

After decades of undertreatment of pain, the most recent audits have shown clear progress in the last 20 years [3]. The systematic and generous use of morphine played a role in this progress. However, morphine, the standard of reference for analgesia, has shown its limits: less efficacy for movement-induced pain, potentially debilitating side effects, delay in post-operative rehabilitation, dose-dependent hyperalgesia as

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a source of both acute and chronic pain, immunomodulation that may have a negative impact on post-operative infection or cancer [1], and, finally, some concern about possible neurotoxicity [4]. Therefore, modern-day analgesia has moved toward a morphine-sparing approach. Indeed, the principle of balanced analgesia described by Kehlet et al. in 1990 [now prevails for post-operative analgesia]. The goal since 2015 is optimal analgesia that allows rapid rehabilitation without sequelae or pain chronicity through the use of drugs and/or techniques that allow minimization of opioids.

What are the needs in 2016?

Need to optimize post-operative management

Despite progress made over the last 20 years, benchmarking investigations make it clear that there is a great disparity in the treatment of pain. Thus the data in the European PAIN OUT study that compared 30 European sites, found a ten-fold variation in the time patients spent with severe pain after major surgery [6]. A very large German survey of more than 70,000 patients classified post-operative pain after 129 types of surgical procedure [7]. This study helped to highlight that some surgeries currently considered as minor (appendectomy, cholecystectomy, laparoscopy) are followed by severe pain and are ranked in the top quarter of the most painful surgeries, exceeding the pain reported for major surgeries where the introduction of invasive pain-suppressive treatments has resulted in a lower level of pain [7]. These results are explained by the fact that our analgesic strategies rely more on the idea of expected pain rather than on adaptation of analgesic strategies to the actual pain felt by the patient.

Need for pre-operative detection of the risk of pain chronicity

Nociceptive pain relates directly to the noxious stimulus of tissue trauma. When such trauma cannot be avoided (*e.g.*, during surgery), the body calls upon protective mechanisms to assist in tissue healing: pain sensitivity is increased to avoid further injury [8]. This state of hypersensitivity to pain is termed hyperalgesia. It contributes not only to the experience of acute post-operative pain but also to the development of pain chronicity. There is a correlation between the surface area of post-operative hyperalgesia and the incidence of chronic pain at 6 months [9,10]. Since the first publication on the subject in 1998, literature reports have identified risk factors for hyperalgesia and CPSP. Young age, the presence of pre-operative pain, the type of surgery, multiple interventions, and the existence of psychological vulnerability [2,11,12] are risk factors that can be identified pre-operatively. The presence of opioid-dependent pre-operative pain is the best-demonstrated factor. Variability in individual patient pain sensitivity and the risk of CPSP linked to genetic factors have been proposed but conclusive data are not currently available [12]. Finally, predictive scores of CPSP have been developed that include age, type of surgery, level of anxiety, size of the incision, and pre-operative pain levels [13,14], but their use in daily practice is not necessarily easy. One can, however, assess the above-mentioned risk factors during the pre-anesthesia or pre-surgical consultation in an attempt to detect at-risk patients at risk and adapt their peri-operative management.

Need to detect early factors for chronicity

Chronic post-operative or post-surgical pain is often underdiagnosed. It is defined as pain that persists 3—6 months after surgery. It can occur following various surgical procedures (inguinal hernia repair, Caesarean section, thoracotomy, etc.) and incidence varies from 10 to 80% of patients [9]! Incidence of chronic pain ranges from 10% to 60% after mastectomy, 0 to 37% after inguinal hernia repair, and >50% after thoracotomy [11]. The Norwegian study cohort TROMSO was the first to quantify the impact of CPSP in the general population: 18.3% of the population undergoing surgery in the previous 3 years had moderate to severe CPSP, half of whom had neuropathic pain; in two-thirds of the cases, the CPSP was localized to the extremities [15].

Currently, there is a real discontinuity in patient follow-up from hospital discharge to the late diagnosis of chronic post-operative pain. Yet it is well established that certain characteristics of post-operative pain such as intensity, duration and neuropathic symptoms are predictors of chronicity. CPSP is associated with high levels of early post-operative pain and significant consumption of post-operative analgesics [2,16]. In addition, hyperalgesia is generally a risk factor for CPSP [10]. Besides the tissue trauma and subsequent inflammation, we must remember that the use of peri-operative opioids is a major source of hyperalgesia. Since the work of Joly et al. [17], it is known that anesthesia that includes high intra-operative doses of opiates causes more post-operative hyperalgesia. Opiates amplify the pain awareness process through N-methyl-D-aspartate (NMDA) receptors. Thus, major surgery that involves considerable tissue trauma and high doses of intra-operative opiates causes a significant clinically detectable hyperalgesia [18] that may result in high post-operative pain levels and may lead to CPSP.

Furthermore, recent studies have shown that the presence of neuropathic pain in the immediate post-operative period was significantly associated with the development of chronic neuropathic pain [19,20]. These studies have also shown that the more neuropathic symptoms (burning, electrical tingling, dysesthesia, etc.) are present, the greater the likelihood of developing high-intensity chronic neuropathic pain. The use of the DN4 score [21], facilitates detection of the neuropathic nature of pain, and should be systematically proposed for any persistent post-operative pain.

What are the up-to-date measures to ensure an optimal analgesia without medium-term consequences or the risk of developing chronic pain?

The French Society of Anesthesia and Intensive care (SFAR) website has published Formal Recommendations by Experts (FRE) on the management of post-operative pain [22]; these clearly and specifically recommend that the possibility of CPSP be considered. Surgical technique can certainly influence the incidence of chronic pain. It is also recommended that risk factors for chronic pain be identified pre-operatively, principally the intensity of pre-operative pain and type of surgery.

Reduce tissue trauma

Some modifications in surgical technique have been shown to be useful: thus abandoning the Pfannenstiel incision in favor of the Joel Cohen incision for cesarean section allows a reduction in the consumption of analgesics and levels of post operative pain [23]. Likewise, laparoscopy has reduced the risk of CPSP during inguinal hernia repair. Whatever the type of surgery, chronic pain occurs more commonly in cases where nerves are injured intra-operatively [2]. The simple insertion of a rib spreader for thoracotomy is sufficient to induce lesions of the intercostal nerves [24].

Intra-operative analgesia avoiding opioids: ''opioid-free anesthesia''

The widespread use of high doses of opioids has showed its limitations: reduced efficacy for movement-related pain, dose-dependent side effects that can be very debilitating for the patient and may delay post-operative rehabilitation, dose-dependent hyperalgesia (a paradoxical source of both acute and chronic pain), immune modulation that may have a negative impact on infections and cancer [1], and, finally, concern about possible neurotoxicity [4]. Therefore, modern intra-operative and post-operative analgesia is based on the principle of morphine sparing. This has shaped the current attitude of post-operative multimodal analgesia. The same attitude applies intra-operatively. The deleterious side effects of morphine derivatives used during general anesthesia are identical to those described for post-operative morphine and are dose-dependent. Historically, the administration of high-dose morphine intra-operatively was the simplest and most effective method of reducing the dose of hypnotic agents while providing hemodynamic stability. But this paradigm is now being challenged. Intra-operatively, the goals of hypnosis, hemodynamic stability, patient immobility, and pre-emptive treatment of post-operative pain are achievable with modern techniques and drugs, without the need for opioids. Morphine-free anesthesia requires a multimodal approach. Loco-regional anesthesia (LRA) in combination with general anesthesia is, of course, the technique of choice. Morphine-free anesthesia is classically carried out with the help of LRA. Indeed, blocking of nociceptive afferent nerves and the sympathetic system is fully ensured by LRA. Systemic administration of a variety of anesthetic drugs including ketamine, lidocaine, anti-inflammatory drugs (NSAIDs and dexamethasone), and alpha-2 agonists drugs (dexmetedomidine) reduces the need for peri-operative opioid administration.

- The use of anti-hyperalgesic agents is highly recommended [22]. Ketamine helps prevent post-operative hyperalgesia by antagonizing NMDA receptors. Several meta-analyses have reported the beneficial effect of ketamine on the intensity of post-operative pain and consumption of analgesics [25]. Ketamine reduces peri-cicatricial allodynia, induced pain and pain six months after laparotomy [26]. Gabapentin also appears to have similar effects but there are not enough data to draw definitive conclusions.
- Intravenously-administered Lidocaine blocks sodium channels and peripheral neural discharges excited by nociceptive stimuli, inhibits NMDA receptors, and has anti-inflammatory properties. In clinical practice, all these effects translate into a reduced need for hypnotic agents, improved analgesia, morphine-sparing, reduced length of stay, more rapid resumption of intestinal transit, reduction of nausea and vomiting, and faster post-operative rehabilitation [27]. This has been confirmed in various types of surgery including abdominal and spinal surgery.
- The use of dexmedetomidine allows a reduction of halogenated anesthetic gases while permitting an identical depth of anesthesia, morphine-sparing and improved analgesia [28]. Reduction of morphine use results in a significant reduction in post-operative nausea and vomiting (PONV): Ziemann-Gimmel et al. [29] showed a 17% reduction in the risk of PONV when comparing intravenous anesthesia combining propofol/dexmetedomidine/ketamine *vs.* inhalation anesthesia with opioids. An important benefit of morphine-free anesthesia seems to be emerging in the literature even though evidence is still limited.

Post-operative analgesia with minimization of opioid consumption

The principles of balanced analgesia described by Kehlet et al. in 1990 [5] are now prevalent in post-operative analgesia as well. Prescription of a combination of several different classes of analgesic is the rule today in order to optimize analgesia while limiting the adverse effects attributable to the various analgesics agents. Thus, the RFE published by SFAR in 2009 [22] specifically recommend combined use of at least one non-opioid analgesic (NOA) when post-operative morphine is administered systemically. The simultaneous use of several analgesics aims to improve the overall desired effects or to obtain a better balance between the analgesic effects and potential side effects. A rational analgesic strategy should combine the use of medications that act on different targets involved in the identified pathophysiological mechanisms. A classic example is the combination of an NSAID that reduces peripheral prostaglandin production with an opiate that acts on central pain receptors. Morphine sparing also reduces dose-dependent side effects.

In general, LRA techniques allow a >60% decrease in morphine use. Thus the incidence of CPSP after thoracic surgery with post-operative epidural analgesia is only 10—20% *vs.* 30—40% on average for all techniques combined [30]. Epidural analgesia also reduces peri-cicatricial allodynia related to laparotomy incisions [31].

Conclusion

The last 20 years have seen significant progress in the treatment of peri-operative pain. The detection of new clinical entities such as post-operative chronic pain and the negative consequences of excessive use of opioids have redefined the issues. The goal in 2016 is a high-quality peri-operative analgesia that minimizes the use of opioids and thereby enables rapid rehabilitation.

Disclosure of interest

The authors declare that they have no competing interest.

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