A Short Review on the Current Status of Multimodal Analgesia for Postoperative Pain: How Recent Findings Suggest a Change in Perspective

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Abstract: Postoperative pain (POP) management is still a challenge in everyday clinical practice, and despite therapeutic improvements of the last two decades, it still remains undertreated. POP influences peri-operative comorbidities and outcome, and can also become chronic, affecting patient's quality of life and increasing costs for the health system.

POP is complex, as it is not purely inflammatory or neuropathic, but mixed; a multimodal approach combining different drugs and techniques (acting on different pain components) is mandatory, and is demonstrated to be a therapeutic approach to improve patient's outcome. In this short review we present new evidences regarding different drugs and techniques currently used in multimodal analgesia protocols, and we explain how these evidences should lead to a change in perspective. Physicians should plan perioperative pain treatment to treat not only pain itself, but choosing the best treatment according to patient history, concomitant pathologies and type of surgery, in order to reduce perioperative comorbidities, chronic pain incidence and, thus, improving outcome.

Keywords: Post-operative pain, multimodal analgesia, regional anesthesia, surgical outcome.

Postoperative pain (POP) management is one of the main challenges for anesthesiologists, and, despite many efforts, it still remains undertreated [1].

POP is strictly related to postoperative comorbidities and is able to influence patients' outcome; pain can also become persistent, affecting patient's quality of life and increasing costs for the health system [3-6].

POP is a complex phenomenon, as it is not purely inflammatory or neuropathic, but mixed, involving different neurophysiological components and combining spontaneous and incidental pain nociception. Thus, a rationale approach to pain treatment should combine different tools against every single aspect of nociception; multimodal analgesia is based on this philosophy: to combine different drugs with different actions to achieve optimal pain relief minimizing drug-related side effects. Non-opioid drugs, weak and strong opioids, regional anesthesia and adjuvants are the main weapons to fight pain, even though they could give different impact on patients' outcome [3,7].

In 1985 American Society of Anesthesiology already considered multimodal analgesia a key tool in POP management [8]. It has been assumed that sufficient pain relief will improve the surgical outcome with reduced morbidity, need for hospitalization and convalescence, and there is a common consensus that optimal (dynamic) pain relief is a prerequisite for early postoperative recovery. In the last 15 years it has been clearly demonstrated how a multimodal approach positively influences patient's outcome after surgery [9]: multimodal analgesia, acting on different pain components and reducing surgical stress after surgery, provides optimal relief with less pain-related comorbidities (respiratory, cardiac and thrombotic complications, nausea and vomiting, ileus, catabolism enhancement, cognitive dysfunctions), and facilitates enhanced recovery (early feeding, early mobilization and rehabilitation, reduced length of hospital stay) [2].

Nevertheless, research towards multimodal analgesia produced significant improvements, with new drugs/techniques now available, or gaining renewed interest thanks to the introduction of new equipment, particularly ultrasound. For this reason, considering the state of the art, a change in perspective is probably required: what we have considered so far as *gold standard* for specific indications, could be re-evaluated

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considering that new modalities to fight pain are available, sometimes associated to less side effects.

The aim of this short review is not to further demonstrate the role of multimodal analgesia or to compare efficacy of specific analgesic drugs or techniques, but to present the existing literature about main analgesic tools, with specific focus on those that had significant improvements in recent years. We try to present recent advantages in multimodal analgesia that could help physicians and researchers to re-define the concept of *gold-standard* for different surgical patients, considering the influence of perioperative analgesia both on short and long-term outcome.

METHODS

We identified reports of studies assessing the use of different drugs and techniques included in multimodal analgesia protocols. Pubmed databases was searched from 2000 to November 2013 using the terms: "non steroidal anti-inflammatory drugs", "acetaminophen", "intravenous lidocaine", "paravertebral block", "continuous local anesthetic wound infusion", "TAP block", "gabapentin", "magnesium", "clonidine", "peripheral nerve blocks", "opioids" AND "postoperative pain", "acute pain", "chronic pain", "persistent pain", "multimodal analgesia".

Additional reports were identified from reference lists of retrieved papers or, even if not listed on Pubmed, from proceedings (published on European Journal of Pain Supplements) of an international scientific meeting on Pain Therapy held in Italy in the last 6 years. Only papers in English were considered. Due to the large amount of retrieved publications, and to the fact that our paper is not intended to be a comprehensive review of all multimodal analgesia, we decided to choose only those papers providing data in support of the "change in perspective" suggested in our manuscript; we made a selection to provide the reader with references which are reviews or meta-analyses themselves (when available) in order to provide the most comprehensive view of each issue.

Recent Findings in Literature: What's New about Well-Known and Extensively Used Drugs and Techniques

Research towards multimodal analgesia produced a large amount of data in the last two decades, bringing significant improvements in our knowledge and in our ability to treat patients; some of these data showed that new technique are available as valuable alternatives for pain relief, other gave a deeper insight to drug-related well-known side effects, or showed new side effects potentially affecting treatment choice.

We will focus on findings that could have a higher impact in changing our future clinical practice.

Non Steroideal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are one of the main drugs for multimodal analgesia [10]. They have analgesic, anti-inflammatory and antipyretic actions, based on inhibition of cyclooxygenase (COX) synthesis, with different selectivity for COX-1 (innate) and COX-2 (induced). Nevertheless, NSAIDs' widespread use can be limited by their well-known side effects, based on their non-specific action on COX, interfering on platelet (hemorrhagic complications), gastric (gastric complications) and kidney function (kidney damage).

COX-2 selective inhibitors were developed to overcome these limits, but concerns about cardiovascular toxicity raised [11]. However, new evidences are available about this issue: results of the basic research show that the increase for cardiovascular risk not only depends on the ratio of the inhibition of the thromboxane and prostacyclin but also on other mechanisms (including blood pressure elevation and COX-independent mechanisms) [12]; available clinical data indicates that the entire substance group of NSAIDs may cause an increased risk for cardiovascular/ thromboembolic events [13]. Thus, different parameters have to be considered in NSAIDs choice, which should be based on patient's comorbidities, risk for complications and the main effect we want to achieve to control POP (anti-inflammatory or analgesic), also considering the similar analgesic efficacy of NSAIDs and acetaminophen if combined with morphine Patient-Controlled Analgesia (PCA) [13].

Opioids

Weak and strong opioids are used in a wide range of surgical settings from moderate to severe pain (in which they are mandatory, particularly when regional anesthesia can not be performed). However, we are in a constant contradiction between the need for opioids and fear for side effects: the most frequent in the postoperative setting include nausea, vomiting and ileus, while sedation and respiratory/cough reflex depression, pruritus, urinary retention, tolerance and hyperalgesia are not so common when used in a short time period. However, if opioids are needed, PCA is still advocated to be the recommended way of administration after surgery, considering its better

efficacy comparing with continuous administration [14,15]. Noteworthy, some problems are still associate to PCA [16-18], and new strategies have been developed for a safe and efficient opioids' use after surgery: fixed combination of oxycodone/naloxone [19] or morphine-oxycodone [20], tapentadol [21], a new transdermal patch for fentanyl patient-controlled release [22,23], sublingual and intranasal devices for opioids delivery [24,25]. Some of these strategies have been validated and are already available for clinicians and patients, while others still remain off-label indications or not promptly available for daily use.

Research has also recently brought new evidence about opioid-related side effects, potentially able to influence long-term outcome, beyond pain itself.

Opioids have depressant actions on the immune system [26], reducing natural killer (NK) cells activity, impairing surgery-induced T cells proliferation, decreasing the cytotoxic T-lymphocytes (CTL) killing activity, and favoring metastasis formation [27-30]. Furthermore, antigen presentation is impaired by even brief exposure to morphine [31] reducing the patient's ability to kill cancer cells. Opioids also have effects on the biology of several cytokines and growth factors, seeming to favor a Th2 over a Th1 response (a more cancer-protective immune pattern) [26]; finally, cancer cells express opioid receptors on their cytoplasmic membranes and activation of these receptors could induce transactivation of vascular endothelial growth factor receptor (VEGF) that leads to angiogenesis and tumor proliferation [32-33]. All these findings suggest a potential role of opioids in facilitating distant malignant cells proliferation and expansion after oncologic surgery: further studies are needed to confirm preliminary results, but in the future we will maybe need to consider other strategies to fight postoperative pain in cancer patients. In this context, we must not forget that pain itself is well known as immuno-suppressant: effects of painful experiences on immunity and the impact of surgery on immune function in both animals and humans have been studied extensively. In general, both acute experimental and postsurgical pain have been shown to suppress immune functions [37-40]: proper pain treatment is always needed also to reduce immune impairment and, if no other choices are available, morphine (with all its risk) should be considered.

On a long-term perspective, results from recent studies regarding opioid-related central nervous system (CNS) plasticity are worth to be mentioned: opioids consumption has been related to structural changes (grey matter increase-decrease) in different brain regions [34], and experimental studies on patients using opioids chronically have demonstrated these changes as irreversible, not regressing after opioid suspension [35].

Finally, a bone-fracture model study in rats have demonstrated that morphine can hamper bone healing by reducing callus formation and maturation [36], thus suggesting a new line of research to understand possible consequences in orthopedic surgery.

Anti-Hyperalgesics Drugs

Regarding opioids, it has to be considered that they could induce short-term analgesia and long-lasting hyperalgesia. To prevent this condition, some authors recommend associating opioids with antagonists of the excitatory neurotransmission, such as ketamine [41] or other adjuvants.

Ketamine

Ketamine is a competitive inhibitor at the NMDA site of the excitatory glutaminergic transmission and reduces incidence of postoperative residual pain [42-45]. It is also documented to be an anti/pro-inflammatory substance helping to restore inflammatory homeostasis after trauma or sepsis, through interaction with their nuclear transcription precursor (the nuclear factor kB) by a specific action on the purinergic receptors (adenosine 2A) and/or a reinforcement of the anti-inflammatory cholinergic reflex [46-48].

Clonidine

The α2-adrenoceptor agonists are interesting drugs to be considered for multimodal analgesia and anti-hyperalgesia, as they potentiate the effect of central descending inhibitory pathways on pain perception, reducing windup phenomenon [49]. Systemically, these drugs potentiate the analgesic effects of opioids (by a factor 4) without increasing their hyperalgesic properties [50]. Spinally, these drugs reduce the area of secondary hyperalgesia when compared with bupivacaine or placebo, and lower the incidence of CPSP after colonic surgery [51].

Magnesium

Animal studies demonstrated that magnesium is an antagonist of N-methyl-d-aspartate glutamate receptors, which can alter the perception and duration of pain [52]. A recent meta-analysis evidenced that systemic administration of perioperative magnesium

reduces postoperative pain and opioid consumption [53]; major doubts remain about its use through the neuraxial route, despite the analgesic efficacy, due to an unclear central nervous system toxicity [54].

Gabapentinoids

They act by binding the $\alpha 2/\delta$ subunits of voltage-gated calcium channels, preventing the release of nociceptive transmitters, including glutamate substance P and noradrenalin. In recent years, gabapentin has been widely used as an adjuvant for treatment of acute postsurgical pain; several meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain [55-57], even if concerns still exist about its ability to delay patients' recovery. Pregabalin has also been found to be effective in reducing acute postoperative pain [58-63]. Focusing on long-term outcome, a recent review supports the view that perioperative administration of gabapentin and pregabalin are effective in reducing chronic postsurgical pain (CPSP) incidence, but it also suggest that better-designed and appropriately powered clinical trials are needed to confirm these early findings [64].

Intravenous Lidocaine

Local anesthetics have demonstrated anti-inflammatory [65,66] and analgesic effects. Intravenous lidocaine was demonstrated in a recent meta-analysis to be associated with lower pain scores, reduced postoperative analgesic and intraoperative anesthetic requirements, as well as faster return of bowel function and decreased length of hospital stay [67,69]. These findings suggest that, when epidural anesthesia is contraindicated, intravenous infusion of lidocaine could be an effective alternative in a multimodal program; preliminary results in non-accelerated programs are encouraging, even if they need to be confirmed in "*fast-track"* studies [70] to clarify the role of IV lidocaine in ameliorating outcome after surgery [2].

On an outcome point of view, it has been recently demonstrated a protective effect of lidocaine on chronic post surgical pain after breast surgery [68]; new studies are needed to confirm these data, but intravenous lidocaine could be an effective, safe and low-cost method to prevent CPSP and improve patients' quality of life after surgery.

Regional Anesthesia

Regional anesthesia is one of the most important features of multimodal analgesia for its great efficacy against dynamic pain and central sensitization [71].

Literature has confirmed the evidence of both a high analgesic efficacy and improved outcome associated with regional techniques [72-77]; beyond analgesia epidural block has been demonstrated to have widespread activities in preventing many stress-induced physiological reflexes, reducing postoperative comorbidities and enhancing recovery after surgery [2]. Also peripheral nerve blocks (both as a single shot or continuous technique) have provided good evidence about their analgesic efficacy and opioid sparing effect, enabling early ambulation and becoming a first line indication to enhance patients recovery in major orthopedic surgery [2,78].

However, regional techniques means also risks, and the risk–benefit analysis must consider the incidence of complications [79]: nowadays the question is: "*Is epidural still the gold-standard for every type of surgery?*" [80]. This is a new perspective, in which we should choose the most suitable technique according both to patient's features (history, surgical setting, expected recovery) and perioperative/long-term outcome (and *not only* focusing on analgesia itself); in this context, side effects potentially affecting recovery must be carefully considered, to find the best analgesic technique in every specific surgical setting.

Considering the risk of severe complications, "new" regional anesthesia approaches have been studied in recent years as a safer alternative to epidural analgesia.

Paravertebral Block (PVB)

PVB is an old technique that has gained renewed interest in recent years in unilateral surgery thanks to the introduction of ultrasound, which permits to recognize anatomical structures and to avoid complications [81-83]. A recent meta-analysis showed that PVB is as effective as epidural blocks for perioperative pain management with less side effects [84]: the authors demonstrated that in thoracic surgery (typically associated to severe pain and marked impairment of the respiratory function) PVB and epidural are equally effective in terms of pain values, but incidence of pulmonary complications, nausea and vomiting, urinary retention, hypotension and rate of failed block were lower in PVB; all these findings brought the authors to finally state that "PVB is recommended for major thoracic surgery"

Transversus Abdominis Plane (TAP) Block

TAP block regained great interest thanks to the introduction of US-guidance [85]. It provides excellent

analgesia of the anterior-lateral abdominal wall, and has been demonstrated to reduce morphine requirements in different types of surgery [86,87]; continuous subcostal TAP block resulted in analgesia comparable to epidural when part of a multimodal protocol [88] and showed to provide opioid-sparing effect in bariatric surgery [89].

Continuous Wound Infusion (CWI)

CWI of analgesics into the surgical wound is a simple and safe technique, even though there are conflicting results about its real efficacy [90]. There are several important issues to be taken into account to explain heterogeneous findings about CWI: evidence shows that the catheter must be sub-fascial to provide effective analgesia, and there is still a debate about best doses and concentrations of local anesthetic and adjuvants (as NSAIDs) [91,92] for each type of surgery. Despite these limitations, CWI seems a promising analgesic tool without important side effects; doubts need to be solved to better determine its role in postoperative multimodal analgesia for each specific surgical setting, and to define the possible effect on CPSP prevention. Peripheral inflammation in the surgical wound leads to peripheral sensitization and primary hyperalgesia, so the primary target of analgesia should be the origin of nociceptive inputs, i.e. the surgical incision itself. Furthermore, sustained inflammation and nociception lead to central sensitization and secondary hyperalgesia: incisional pain model has clearly demonstrated that pre-incision analgesia (i.e. preemptive analgesia in clinical practice) is of little interest because when the effects of analgesic treatment abate, the wound itself is able to restart sensitization processes [93]. By consequence, effective postoperative treatments should cover the entire perioperative period; these considerations support the role of CWI not only on acute pain, but, potentially, also on mechanisms underlying CPSP development: results from ongoing clinical trials (NCT02002663) could clarify CWI protective effect on CPSP.

Despite their analgesic efficacy, evidence is still lacking about the ability of PVB, TAP block and CWI to enhance patients' recovery after surgery when inserted in "*fast-track"* programs; these techniques are promising alternatives to epidural for postoperative pain control with less risk of major side effects, even if their effect on long term outcome has to be better determined.

Finally it's noteworthy that a variable amount of local anesthetics administered during peripheral and neuraxial blocks is absorbed to systemic circulation, and this amount can be very different between patients [94]; part of the analgesic effect of all the abovementioned regional techniques could be ascribed to the systemic analgesic and anti-inflammatory effect of the absorbed amount of local anesthetics.

How Perioperative Treatment can Influence Long-Term Outcome: The Concept of Protective Analgesia

Protective analgesia is strictly connected with Chronic Post-Surgical Pain (CPSP), defined as pain that develops after surgery, of at least two months' duration, while other causes for pain have already been excluded, and with a type of pain different from a preexisting one [95]. Persistent pain after surgery is currently regarded as an important outcome as it may reflect the quality of perioperative cares provided to the patients and a series of papers have investigated the topic [96-100].

Chronic post-surgical pain has been recognized as a complication after different surgical procedures, with different incidence depending on type of surgery; furthermore 2% to 10% of CPSP patients evolve toward developing severe chronic pain. Patho-physiology of chronic pain is not totally understood, but CPSP syndrome results mainly from persistent inflammatory response and neurological "dys"function that could create secondary hyperalgesia and allodynia [49]. Long-lasting noxious stimulations, inflammation or damages to the neuronal tissues, give rise to a neuronal hyper-excitability that is, normally, relatively short lasting and associated with reversible plastic changes in neuronal connectivity, involving altered expression and trafficking of ion channels and of synaptic transmitters [101-103] neuro-immune interactions [104,105] and neuronal death [106]. In some circumstances, important and not reversible changes in neuronal connectivity take place, with a marked reduction in local segmental inhibitory transmission at spinal and central level [106] leading to CPSP.

The aim of protective analgesia is to maximally reduce the importance of primary and secondary hyperalgesia, that is, to maximally reduce the excitatory input coming from the damaged periphery to the central nervous system and to put the central nervous system in a reduced reactive state. For this purpose, it is advocated to use strong analgesic techniques combined with drugs acting specifically on secondary hyperalgesia.

Thus, a multimodal strategy acting on different pain components is mandatory: NSAIDs (against pain and

hyperalgesia associated with tissue trauma and inflammation), regional techniques (strong afferent blockade and dynamic pain control), opioids (action on spontaneous pain and primary hyperagesia) and all anti-hyperalgesic techniques should be combined in order to prevent central sensitization and CPSP development, particularly in high risk patients [107]; starting from the pre-operative period, to be protective means a *"detect, prepare, treat"* approach: we need to detect patients more at risk of CPSP, prepare them and, finally, use the best analgesic techniques to prevent both acute and chronic pain [100] .

CONCLUSION

Different drugs and techniques have been validated to control acute pain: new approaches are now available to face pain itself, particularly when combined in multimodal protocols to achieve higher analgesic efficacy with less side effects; some of them, in consideration of their better safety profile, have been proved to be valuable alternatives to the gold standard epidural analgesia.

However, multimodal analgesia has to address its effort to protect patients not only from pain itself but also from the whole perioperative stress, in order to reduce comorbidities. In this sense, a change in perspective is needed: the choice is no more "*epidural or not*"; the choice towards a specific drug or technique must take into account both patient history, concomitant pathologies and type of surgery: this evaluation will allow to be actually aware of the risk-benefit ratio, and to plan treatments according to each patient and its desired recovery, with the final aim of patient's outcome and not only of pain relief itself.

This concept should be extended to CPSP: in the past decades research on multimodal analgesia changed its focus from immediate postsurgical pain to the entire peri-operative period. It's now time to go further: we need to focus on patients at home, after they have left the hospital; physicians should choose techniques and drugs (and combine them) in order to maximally protect patients from sensitization and pain chronicization, thus improving long-term outcome.

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