Chapter 3

Is Chronic Post-Surgical Pain Preventable?

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http://dx.doi.org/10.5772/intechopen.79500

Abstract

Chronic post-surgical pain (CPSP) is a common problem following surgery. It has significant impact on the patients' quality of life, chronic pain treatment services and resources in general. The prevalence of CPSP ranges between 5 and 50% of all surgical patients, but severe CPSP is present in less than 10% of the patients. The recognised potential risk factors for CPSP are young age, female gender, overweight, psychological factors, genetic tendency, pre-operative pain, surgery-related factors and severe post-operative pain. Hence, early identification of patients at risk will help to reduce the proportion of patients who are likely to develop CPSP. Different modalities of treatments or interventions are used to prevent the CPSP. These modalities include pre-emptive use of gabapentin, pregabalin or SNRIs, perioperative administration of ketamine, NSAIDs and steroids. In addition, the following interventions have been studied: surgical technique selection, regional and local anaesthesia, intrathecal administration of morphine and multimodal analgesia. Since the present evidence of these interventions is inconclusive because of methodological issues, further studies are still needed to develop more effective and evidence-based strategies to prevent CPSP.

Keywords: chronic pain, post-surgical pain, prevention, gabapentin, anaesthesia

1. Introduction

Millions of people undergo surgical interventions annually all over the world. A majority of them recover within a few days after surgery and go back to resume their routine daily activities. However, it is estimated that one out of five patients who undergo surgery do not completely recover and develop chronic post-surgical pain (CPSP) [1]. Indeed, surgery was identified as one of the most common causes for chronic pain among patients who attended pain clinics [2]. Although there is no universally accepted definition for CPSP, it is generally

described as pain which persists after a surgical procedure beyond the surgical wound-healing time. There was no consensus about the time frame which defines chronicity following surgery, and this ranged from 1 month to 1 year [3]. However, more recently, an International Association for the Study of Pain (IASP) task force has defined the period as 3 months which is consistent with the definition of chronicity in other types of chronic pain [4]. In the quest for a clearer definition, Macrae proposed a four-point definition for CPSP. CPSP becomes chronic if (1) the pain has developed as a consequence of surgery, (2) its duration is at least 2 months, (3) no other explanation exists for the pain and (4) the pain is not a continuation of a pre-existing chronic pain condition for which the surgery was performed [5].

Studies have shown that the incidence of CPSP ranges from 5 to 50% [6]. Major surgical procedures such as mastectomy are associated with a higher incidence (20–50%), whereas minor procedures such as hernia repair are associated with a lower incidence (5–35%) [6]. Anatomically, the most affected sites are chest wall, breast, hip joints and iliac crest bone [1].

As any type of chronic pain, CPSP is considered as a major public health problem. It has a huge impact on the quality of life and psychological well-being. Chronic pain has been shown to affect mood, sleep and basic daily activities [7]. In severe cases, it can lead to disability. It is also associated with a heavy socio-economic burden as a result of direct costs which are related to treatment and indirect costs such as lost wages and unemployment [8]. Prevention is far more important than treatment here because of the incurable nature of CPSP and its association with neuropathic type of pain which is always difficult to treat.

Hence, the aim of this chapter is to review the pathophysiology of CPSP and to explore the risk factors which contribute to its development, bearing in mind the great importance of early identification of patients who are at risk before surgery. Different modalities of treatments and interventions, which have been used in the context of prevention of CPSP, will be discussed.

2. Pathophysiology

Understanding the pathophysiology of post-surgical pain is crucial for the development of effective approaches to prevent and treat the CPSP. Pain is a psychological sensory experience which is caused by different factors. These factors are nociceptive, inflammatory and neuropathic pain [9]. Two main mechanisms have been described to contribute towards the development of CPSP. These are inflammation and surgical injury to major peripheral nerves [6]. Tissue cutting and handling during any surgery causes the release of sensitising, inflammatory cell mediators. These mediators are cytokines, bradykinin and prostaglandins. These inflammatory mediators activate nociceptors which demonstrate reversible plasticity. Nociceptor stimuli are carried to the dorsal horn of the spinal cord via primary afferent Aδ and C fibres as electrical impulses. Moreover, those electrical impulses will be taken to the cerebral cortex and other higher centres via the contralateral spinothalamic and spinoreticular pathways: the two main ascending pain pathways which lead to the experience of pain. This process leads to the occurrence of peripheral and central sensitisation. The peripheral

sensitisation enhances pain sensitivity at the site of tissue injury. It occurs when the activation threshold of nociceptors is lowered. This type of inflammatory pain, secondary to local excitability, usually subsides once the source of the mediators subsides, as tissue healing occurs or the disease process is controlled. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandin E2 via locally induced cyclooxygenase-2 enzymes and hence reduce peripheral sensitisation and pain. By contrast, the central sensitisation is an excitability of neurons in the central nervous system (CNS). It occurs because of enhanced pain signalling within the spinal cord in the second-order neurons due to ongoing nociceptive input which may last longer than the initial stimulus. Clinically, this manifests as wind-up, long-term potentiation, hyperalgesia and pain secondary to normally non-painful tactile stimuli (allodynia). Wind-up happens with the repeated activation of C fibres. Under normal conditions, due to the action of glutamate at N-methyl-D-aspartate (NMDA) receptors, a magnesium ion blocks the NMDA receptor. However, due to the presence of continuous painful stimuli, the response of second-order neurons to painful stimuli is amplified due to the removal of the magnesium block. This explains the role of ketamine (NMDA receptor antagonist) in reducing

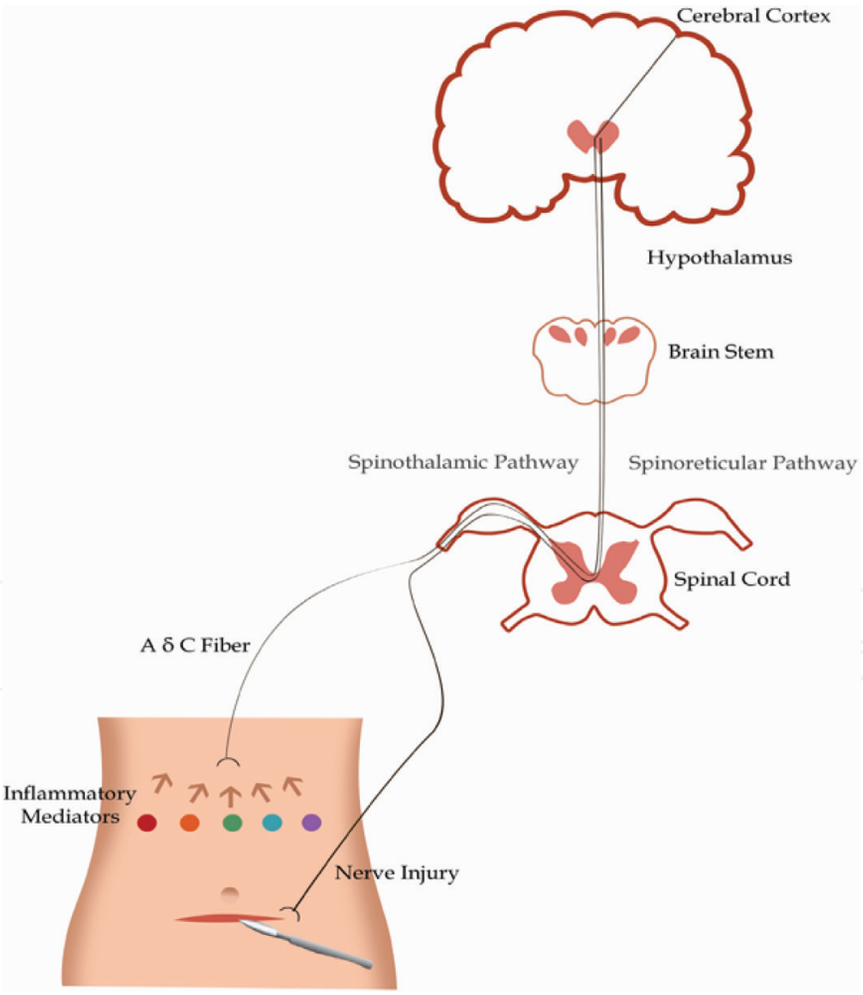

Figure 1. An illustration of the two main mechanisms which contribute towards the development of CPSP (inflammation and nerve damage). The pain pathways depicted here are the ascending pain pathways [10].

or blocking wind-up. The long-term potentiation is the second-order neurons response which last longer than the initial stimulus. Hyperalgesia results from an amplified response to painful stimuli due to both long-term potentiation and lowering of the pain threshold outside of the area of inflammation [10].

Nerve damage is the second major contributor for the development of CPSP. It is very important here to try to explore the mechanisms of differentiation of neuropathic from non-neuropathic pain. In most affected patients, the pain component of CPSP is similar to pain experienced as a result of neuropathic pain [11, 12]. In patients with CPSP, neuropathic pain can occur as a consequence of spontaneous ectopic discharges from damaged nerves and nearby undamaged nerves following nerve injury. Furthermore, disinhibition of pain pathways and facilitation of pain transmission occur due to loss of inhibitory interneurons in the dorsal horn. Hypoesthesia and neuropathic pain are both caused by nerve damage. In addition, the presence of hypoesthesia in CPSP patients confirms the association between nerve damage and CPSP [11, 12]. Thoracotomy is a good example of surgeries which may lead to nerve injury. In thoracotomy, the use of a rib retractor blocks intercostal nerve conduction by 50–100% in segments close to the incision [13]. Moreover, the degree of nerve damage in thoracotomy correlates with the intensity of chronic pain [14]. In conclusion, acute and chronic pain experience is a multifactorial complex process, involving physiological, genetic and psychosocial factors. These factors contribute to the conversion of somatosensory activity into a pain experience, to the amplitude of and reaction to the sensation, and to related changes in mood and behaviour [9] (**Figure 1**).

3. Risk factors

Various risk factors have been postulated to predict the development of chronic post-surgical pain in patients undergoing surgical procedures [9]. These factors are; genetic susceptibility, preceding pain, acute post-operative pain, psychosocial factors, demographic factors and surgical factors. These factors can be classified as patient-related and medical factors or to modifiable and non-modifiable risk factors [6, 10]. Each factor will be discussed separately in the subsequent text (**Figure 2**).

3.1. Genetic susceptibility

Different people respond differently to physiological and clinical pain because of the variation in pain sensitivity. This discrepancy in pain sensitivity is a recognised factor for susceptibility to CPSP and response to analgesia [15–19]. There are strong indications that chronic pain and specifically CPSP are heritable traits and that genetic variation accounts for about half of the difference in pain levels. Studies done on rodents pointed to a strong heritable component of susceptibility to develop neuropathic pain, but the responsible genes have not yet been identified [19–21]. Future exploration of pain genetic may lead towards a remarkable improvement in CPSP treatment and to a more specific and personalised pain medicine [22]. Analysis of patients' DNA sequences of pain biomarkers and their analgesic responses to

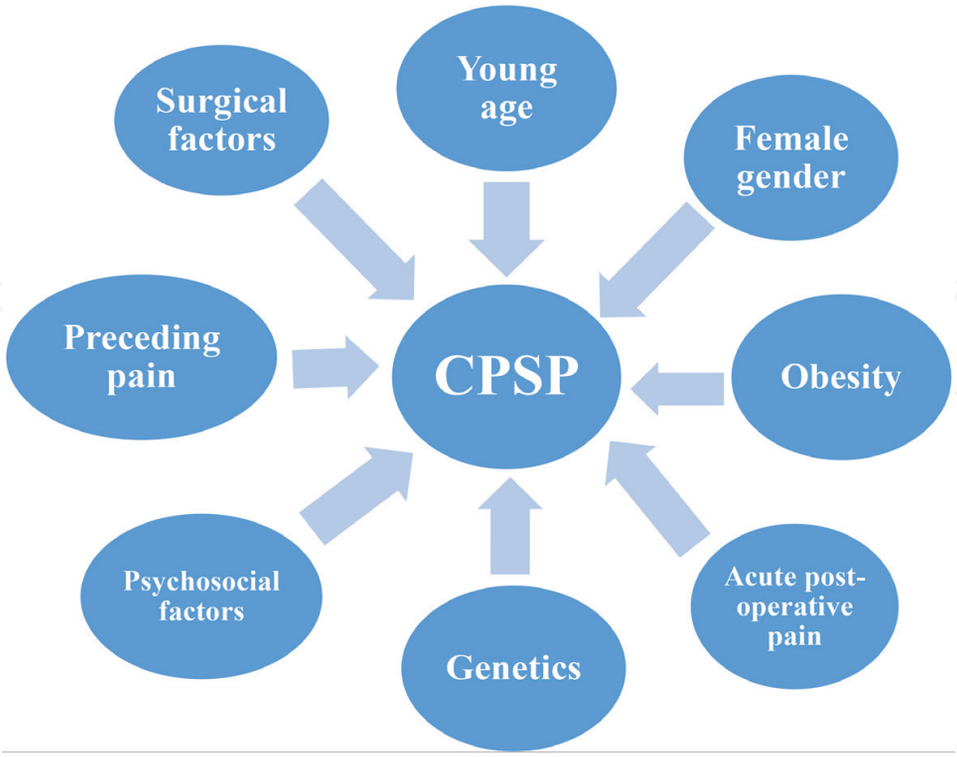

Figure 2. Potential risk factors for CPSP development.

medications will facilitate better understanding of CPSP pathophysiology, and thus it will help to predict a patient's likelihood of developing CPSP even before surgery. In addition, these advances could help in providing effective treatment regimens that will prevent the transition to chronic pain post surgically and help to provide treatment for those who had already developed CPSP. The genetic role is further highlighted by the experimental studies which were done on catecholamine-O-methyltransferase (COMT). In these studies, a correlation was found between the increased COMT activities and the risk of developing chronic temporo-mandibular joint pain [17, 18]. Many investigators have proposed that some clinical disorders such as fibromyalgia, migraine, irritable bowel syndrome, irritable bladder and Raynaud's syndrome could be considered as markers of post-injury chronic pain [23, 24]. In view of the complexity of neuropathic pain, it is very likely that more than one single gene might contribute to the development of CPSP [9].

3.2. Preceding pain and acute post-operative pain

Multiple studies looked at the effect of perioperative pain on the development of chronic post-surgical pain [25–34]. The factors mainly studied were the level of pain immediately before the surgery, the presence of previous chronic pain (lasting more than 6 months) before the surgery and acute pain at post-operative period. The first two factors have independently predicted moderate to intense pain in the acute post-operative period [25, 26]. Three studies, which were done on patients who underwent hernia repair and amputation surgeries, reported that the presence of pre-operative pain at the site of the operation or closer to it can

predict chronic pain after the surgery [30, 33, 34]. In addition, the patients who experienced more severe and long lasting pain before the surgery felt more severe pain after the surgery compared to patients who experienced less severe pain before the surgery [29, 30]. Finally, the last factor studied was the correlation between immediate post-operative pain intensity and the development of chronic post-operative pain [31, 32]. Studies found an increase of two- to threefold risk of CPSP development in patients with immediate post-operative pain [34]. In conclusion, these associations indicate the potential for the prevention of CPSP by aggressive control of pain both pre- and post-operatively and by addressing any chronic pain issues well before planning for any surgery.

3.3. Demographic factors

Younger patients are more likely to develop chronic postsurgical pain than older patients [35–40]. Smith et al. [35] found that chronic pain was seen in 65% of the 30–49 years' age group, in 40% of the 50–69 years' age group, and in 26% of patients older than 70 years. Another study showed that the probability of incidence of CPSP decreased by 5% with each 1 year increase in age in women undergoing breast cancer surgery [41]. Similar findings were seen after hernia repair surgery [36]. The explanation for this higher incidence of CPSP in younger age group is not yet known, but it might be related to the reduction in peripheral nociceptive function with increased age [9]. Besides age, gender has also been identified as another demographic factor. Studies showed that women have higher post-operative pain than men [42, 43]. Furthermore, angina patients with a higher body mass index (BMI ≥ 25) pre-operatively or at the time of surgery were more likely to report CPSP [40]. A young obese female has been described as the triad of high risk to develop CPSP in any patient undergoing surgery [6, 9, 42].

3.4. Psychosocial factors

Previous studies focused on biological factors as predictors for the development of CPSP, but recently, the evidence moved more towards a biopsychosocial model. Multiple pre-operative psychological factors have been studied. These are as follows: negative affective constructs such as anxiety symptoms, depressive symptoms, pain catastrophising, general psychological distress, perceived injustice and sensitivity to pain traumatization [44–57]. Patients with state-trait anxiety are believed to be more hypersensitive and psychologically more reactive to threatening stimuli [44, 57]. Studies showed that pre-operative anxiety and depression are correlated with a higher post-operative anxiety, a higher post-operative pain intensity, higher analgesia requirements and a longer length of hospital stay [44]. Fear of surgery was associated with more pain, poor recovery and a poor quality of life 6 months post-operatively. In one study done on patients who underwent breast cancer surgery, emotional distress like anxiety, depression, illness behaviour and somato-sensory amplification were reported as significant risk factors for higher post-operative acute pain at 1 month, but were not significantly correlated to persistent pain at 3 months post-operatively [58, 59]. On the other hand, a large prospective study with a sample size of 625 patients who had undergone minor, intermediate and major operative procedures found that the fear of the long-term consequences of surgery had predicted an increased level of pain at 6 months post-operatively [60]. This finding

was independent of the type of surgical procedure and other somatic factors. In addition, research has explored the role of health-related beliefs, including catastrophising, in predicting CPSP. Catastrophising, claimed to be a trait-like characteristic, had mainly been assessed in non-surgical chronic pain populations or within the acute post-operative period [61, 62]. Studies reported that pre-operative catastrophising was the strongest independent predictor of pain ratings 2 years after knee arthroplasty [51, 63]. Also, patients who presented with pre-surgical anxiety and pre-surgical pain catastrophising before surgery were approximately twice as likely to develop CPSP compared with controls [64]. Furthermore, perceived injustice and sensitivity to pain traumatization might predict CPSP, but only a few studies were done and further research is still needed [52, 55, 56]. On the other hand, high dispositional optimism, high positive affect, low emotional distress, expectation of pain control and expectations about functional recovery before surgery were significantly associated with a lower pain intensity and fewer physical symptoms following surgery and a lower incidence of CPSP at 4 months in women undergoing breast cancer surgery. Taken altogether, these studies indicate that fostering optimism and enhancing self-efficacy and adaptive behaviours in the perioperative period may help patients navigate through their post-surgical recovery period [58, 65]. However, facing an uncertain future with the presence of health problems, and the requirement from the patient to bear significant pain and functional impairment of important daily activities during the recovery stage from major surgery makes it difficult for patients to always maintain an optimistic attitude [66]. Nevertheless, one study found that lower pre-operative pain self-efficacy scores, which assess a person's confidence in performing general activities despite pain, to be a significant predictor of greater functional limitations, but not pain, at 1 year after total knee arthroplasty [67]. While another study also done in patients undergoing total knee arthroplasty has shown that patients with a higher pre-surgical score on the Patient Activation Measure (reflecting the propensity to engage in adaptive health behaviours) experienced better pain relief at 6 months [68]. In conclusion, fear of surgery was the most consistent psychological predictor of unfavourable outcome, whereas dispositional optimism was related to a better long-term functional recovery after surgery. Further studies are still needed to develop a better understanding of the interaction between CPSP and psychosocial factors.

3.5. Surgical factors

Multiple surgical factors are related to the development of CPSP. These factors are the duration of the operation, surgical technique (laparoscopy vs. open), incision site and type, the experience of the surgeon and the centre where the intervention is performed [6]. In one study, researchers found that patients who underwent operations lasting more than 3 h had more chronic pain, poor functional outcome and poor global recovery at 6 months post-operatively [60]. Generally, the more serious the medical problem or more complicated, the more complex and longer the surgery [6]. Operations with a longer duration are associated with more surgical trauma, more persistent surgical nociception and sustained peripheral injury which in turn would trigger pathological changes in the central nervous system (CNS) [6, 9, 69, 70]. There is a strong relationship between the technique of surgery and the incidence of CPSP. Evidence showed that the more severe the surgical insult or tissue damage, the greater

the risk of persistent pain. Significant differences were seen between open and laparoscopic procedures with a higher incidence of CPSP after open surgeries [71–73]. These findings were observed in different types of surgeries (hernia repair, cholecystectomy and hysterectomy) [71–73]. Less tissue handling and less intervention result in a lower incidence of chronic pain development. Wallace et al. [74] reported that the incidence of CPSP varied from 53% for mastectomy with reconstruction by implant, to 31% for mastectomy only, to 22% for breast reduction. Also, nerve protection during cutting and tissue handling in the operation site or in the neighbourhood during the perioperative period may decrease the incidence of CPSP. This is explained by the fact that nerve injury produces acute and lasting changes not only in the damaged nerves but also in the adjacent intact nerves [75]. Such effects would activate the pain pathways in the CNS, and motor and sympathetic systems [75]. The experience of the surgical team and the centre where the intervention took place have an impact on both morbidity and mortality [76]. CPSP was observed more commonly in surgical units with a lower number of cases and limited experience [76].

4. Potential for prevention

All surgeries carry the risk of CPSP but not all surgeries are medically necessary to be done. Clinicians are looking to moderate the risks of CPSP by identifying patients who are at a high risk prior to the surgical procedure. The identification of high-risk patients can be used to a closer monitoring of these patients and to initiate timely interventions to prevent chronic pain. Assessment tools can be used before surgery to identify the risk probability of developing CPSP by including some predictors such as age, sex, pre-operative pain, type of surgery, incision size, and level of anxiety, among others [77]. Several modalities and interventions have been investigated in the context of prevention of CPSP. Each of these modalities will be discussed in the following parts of this chapter.

4.1. Pre-emptive and preventive analgesia

Pre-emptive analgesia is delivered prior to skin incision. It is initiated before the surgical procedure in order to reduce peripheral and central pain pathways sensitization.

4.1.1. Gabapentin

Gabapentin has a well-established role in the treatment of several neuropathic pain conditions. It is also known to possess anti-nociceptive effects. Such effects result partially from its high affinity for the α 2 d subunit on pre-synaptic voltage-gated calcium channels, which are often upregulated following nerve injury. This leads to the inhibition of calcium influx and to the release of excitatory neurotransmitters, which produce central sensitization and the sensation of pain [78]. The use of gabapentin in CPSP has been extensively studied. The recent evidence indicated that perioperative gabapentin was effective in preventing CPSP. One recent meta-analysis supported the view that the perioperative administration of gabapentin was effective in reducing the incidence of CPSP [79]. Clarke et al. concluded that out of

eight studies, four found that the perioperative administration of gabapentin decreased the incidence of chronic pain more than 2 months after surgery. Six out of the eight studies measured pain 6 months after surgery, and the pooled results demonstrated a moderate to large reduction in the development of CPSP (pooled odds ratio (OR) 0.52; 95% confidence interval (CI), 0.27–0.98; P 0.04) [79]. Two other studies, which investigated the effect of administering 1200 mg of gabapentin before surgery with placebo, reported a reduction in the incidence and severity of CPSP 6 months post -surgery [80, 81]. On the other hand, a systematic review done by Chaparro et al. [82] indicated that the effect of gabapentin was equivalent to placebo in preventing CPSP. Variations were observed in these studies in both the doses of gabapentin which were used (ranged from 300 to 1200 mg per day) and the duration of use (1 h before surgery to 10 days post surgery) [82]. Other variables, which could account for the conflicting evidence for the effectiveness of gabapentin, include diverse surgical procedures and small sample size.

4.1.2. Pregabalin

Pregabalin is a structural analogue of c-aminobutyric acid. It binds to the α 2 δ subunit of the voltage-gated calcium channel which subsequently lead to a decrease in the release of neurotransmitters such as glutamate, norepinephrine and substance P, thereby targeting the putative role of these transmitters in central sensitization in a similar way to gabapentin [83]. Chaparro et al. [82] conducted a systematic review in which five pregabalin trials with long-term pain outcomes were included. Two different dosing regimens were used in these clinical trials, either 150 mg 2 h prior to the induction of anaesthesia and 75 mg twice daily for two post-operative days or a 300-mg single dose pre-operatively followed by a 14-day twice-a-day (BID =50–150 mg). The heterogeneity (I2 of 28.5%) of dosing regimens was problematic with respect to comparing long-term outcomes. Two studies demonstrated a significant benefit of pregabalin as compared to placebo [84, 85]. While the pain outcomes differed at 3 months follow-up, an overall significant effect of pregabalin was reported [82]. Moreover, two additional studies showed a significant reduction in the incidence of CPSP 6 months following both total knee arthroplasty and off-pump coronary artery bypass surgery [84–86]. Therefore, despite the heterogeneity between studies, the available literature favours the perioperative use of pregabalin to prevent CPSP; however, the use of a high dose of pregabalin (300 mg) has been associated with serious adverse effects such as visual disturbances, sedation and confusion during the first day after surgery [85, 87, 88]. These adverse effects settled with continued use, but led to an overall recommendation of using lower doses of pregabalin, with the aim of reducing side effects and hence allowing the successful introduction of physiotherapy and intensive rehabilitation during the immediate post-operative period [85, 87, 88].

4.1.3. Selective norepinephrine and serotonin re-uptake inhibitors (SNRIs)

Venlafaxine hydrochloride is a selective norepinephrine and serotonin re-uptake inhibitor which is widely used as an antidepressant medication. It has a good safety profile as it does not bind to cholinergic, histamine or alpha 1-adrenergic receptors . The efficacy of Venlafaxine, which was administered perioperatively in patients with acute and chronic postmastectomy

pain, has been investigated. The study concluded that venlafaxine significantly reduced the incidence of CPSP at 6 months . Duloxetine is another SNRI medication which has been effectively used in chronic neuropathic pain in patients with diabetic peripheral neuropathy and fibromyalgia [89–93]. However, its role in the prevention of CPSP has not been studied. The current evidence regarding the use of SNRIs in the prevention of CPSP is insufficient, and further studies are still needed.

4.2. Perioperative prevention

4.2.1. Surgical technique

Since nerve damage is considered as one of the major causes of chronic postsurgical pain, minimising nerve injury during any surgery is crucial. Nerve damage can be prevented or minimised by adopting several surgical techniques such as laparoscopic surgery, precise dissection during open surgery, the use of a lightweight mesh for inguinal hernia repair and the use of an intracostal suturing technique. Studies showed that laparoscopic herniorrhaphy and minimally invasive thoracoscopic techniques might decrease the risk of nerve damage and pain when compared with open surgery [94–96]. In addition, the avoidance of nerve damage by making more precise dissection during open surgery or by using the intracostal suturing technique to avoid direct nerve compression was also suggested to reduce the occurrence of CPSP [13, 97]. The use of a lightweight mesh in inguinal hernia repair was intended to produce less inflammatory response which would result in a reduction in the risk of CPSP [98, 99].

4.2.2. Regional anaesthesia

Regional anaesthesia is defined as the use of local anaesthetics to block the conduction of impulses along nerves and to minimise the transmission of signals to or within the spinal cord. Possibly, they prevent central sensitisation by preventing the nociceptive inputs into the dorsal horn [10]. Examples of regional anaesthesia are spinal and epidural techniques which act on the nerve roots. A recent Cochrane review concluded that epidural analgesia and paravertebral blocks were effective in reducing the risk of CPSP at 6 months after thoracotomy and breast cancer surgery, respectively [100], whereas a study by Capdevila et al. [101] did not show any benefit for epidural analgesia in reducing CPSP intensity after open nephrectomy. Spinal anaesthesia has also been shown to be beneficial compared to general anaesthesia in reducing the risk of chronic pain after caesarean section [102]. When comparing the route of regional anaesthesia, similar outcomes for paravertebral block (PVB) and thoracic epidural analgesia (TEA) were achieved [103]. In addition, a comparison between either of these techniques and opioids alone favoured RA [104]. Evidence was in favour for PVB for breast surgery and TEA for lung surgery [105]. The findings of these studies cannot be generalised to other surgical procedures due to small sample size and the experience of the centre where the procedure was conducted. In addition, the studies were heterogeneous in terms of agents used and routes of delivery. Currently, the available evidence suggests that regional anaesthetics as a class are equivocal to placebo for CPSP.

4.2.3. Intravenous lidocaine

Lidocaine is a local anaesthetic which possesses analgesic, anti-hyperalgesic and anti-inflammatory properties. It is usually given intravenously, and it is used as part of a multimodal analgesic regimen. Five studies found significant effects on the incidence of CPSP following the administration of perioperative intravenous lidocaine infusion in several types of surgeries (breast surgery, robot-assisted thyroidectomy and nephrectomy) at 6 months post surgery [106–110]. In conclusion, the available literature supports the use of intravenous lidocaine to prevent CPSP after specific surgical procedures.

4.2.4. Ketamine

Ketamine is a non-competitive NMDA receptor antagonist. The NMDA receptor plays a critical role in both the induction and maintenance of central sensitization and pathological pain. Ketamine is thought to reduce pain and analgesia consumption by preventing NMDA-mediated sensitization of the dorsal horn neurons in the spinal cord [111]. Generally, the available evidence supports the perioperative use of ketamine to prevent CPSP. The effects of ketamine on CPSP were investigated in 14 clinical trials, out of which, 12 trials were of good quality to be included in a systematic review [82]. In most of these trials, pre-incisional loading doses of ketamine, which ranged from 0.15 to 1 mg kg^{-1}, plus an intraoperative infusion was administered. While ketamine was not better than placebo for the reduction of CPSP at 3 months after surgery, a subgroup analysis of trials which only included patients who received ketamine for longer than 24 h demonstrated ketamine's superiority over placebo. A more definitive result was found for ketamine at 6 months following surgery, with an overall significant decrease in the incidence of CPSP. Interestingly, at 6 months following surgery, studies in which patients had received ketamine for less than 24 h demonstrated a reduction in the incidence of CPSP compared to studies in which ketamine was given for more than 24 h. The two clinical trials which were excluded from the systematic review reported no significant differences between ketamine and placebo [81, 112]. The reason for their exclusion was due to lack of reporting of the outcomes of interest. While the use of ketamine to reduce CPSP is empirically promising, the results still remain controversial due to the wide variability in clinical settings, ketamine dose and duration, and reported outcomes. In addition, some of the positive results were obtained using clinical anaesthesia regimens which are not accepted as standard treatments [112, 113]. Overall, the available literature supports the perioperative use of ketamine to prevent CPSP.

4.2.5. Intrathecal administration of morphine

Moriyama et al. [114] studied the effect of intrathecal administration of 0.1 mg morphine in women undergoing caesarean section during surgery. No respiratory depression was reported. The study concluded that although no effect on acute pain was observed, intrathecal administration of morphine significantly decreased chronic pain after surgery by 50% at 3 months post-operatively [114].

4.2.6. Multimodal analgesia

Multimodal analgesia has become the widely accepted modality of treatment for perioperative pain. It is utilising different regimens of different classes of medications according to the type of the surgical procedure and the institute where surgery is performed [115]. The main aim of multimodal analgesia is to target several peripheral and CNS mechanisms to maximise pain reduction, reduce opioids requirements and to decrease opioid-related side effects [103, 107]. A few studies have explored the effects of multimodal analgesia on CPSP prevention. The evidence indicated positive effects at 3 months [116] and at 1 year following surgery [117]. Additional studies are required to study the effects of multimodal analgesia on different types of surgical procedures and to find out whether its preventive effects do indeed reduce the incidence and severity of CPSP.

4.2.7. Non-steroidal anti-inflammatory drugs (NSAIDs)

Prostaglandins are one of the inflammatory mediators activated during surgery which has a possible role in CPSP pathophysiology. NSAIDs are a group of medications which are widely used for their anti-inflammatory properties. They reduce the pain and inflammation through the inhibition of the synthesis of prostaglandins by inhibiting COX-1 and COX-2 receptors. NSAIDs can reduce secondary hyperalgesia and central sensitization [118, 119]. One study showed that Celecoxib (COX-2 inhibitor) had reduced post-operative pain, the need for post-operative opioid analgesia [120] and meanwhile did not inhibit bone healing following arthroplasty surgery [121]. In summary, the available clinical trials are heterogeneous and differ in the following: the type of drug used, follow-up time point and pain outcomes. None of these trials demonstrated a significant impact of NSAIDs on reduction in the incidence or severity of CPSP [122, 123].

4.2.8. Glucocorticoids

Glucocorticoids prevent pain by expressing anti-inflammatory properties and by preventing central sensitization [124]. Three trials studied the effects of perioperative corticosteroid on CPSP. The studies used different types of steroids Dexamethasone, Methylprednisolone and Hydrocortisone. A Cochrane review included these clinical trials. The results were inconclusive, and the heterogeneity precluded any possible meta-analysis. The heterogeneity was due to variations in drugs used, follow-up time intervals and the measured pain outcomes [82].

5. Future directions

CPSP remains as a challenging clinical problem. There are several areas which are promising and can be explored further in the future. Investigators could focus more on the better

identification of individual risk factors and the development of assessment tools before planning for any surgical procedure. There is a hope that we can develop better understanding about the genetics of pain to try to identify responsible genes and develop specific therapies for them. Future studies could be designed to be more procedure-specific to help us understand the mechanistic differences between surgical incisions and pathologies. The role of the multimodal analgesia in the prevention of CPSP should be explored further in view of the positive results of the few available studies. Advance in surgical techniques to try to minimise nerve injuries as much as possible since nerve damage plays a major role in the development of chronic postsurgical neuropathic pain is another promising area for research. Future studies in the field of CPSP should be designed in a better way to include a larger sample size, standard doses and regimens of drugs, and more consistent outcome measurement tools.

6. Conclusion

CPSP is a complex process which is not fully understood. When it occurs, it affects the patients' quality of life. Based on our current understanding of the pathophysiology, nerve injury and inflammation are the two main responsible mechanisms for the development of CPSP. Specific risk factors, which make some individuals at a higher risk than others for CPSP, have been identified. Timely identification of these individuals based on their risk profile allows us to develop appropriate interventions. Several modalities and interventions for CPSP prevention have been investigated. These include pre-emptive and perioperative interventions (**Table 1**). CPSP prevention is an important area for future research in view of the methodological problems with the majority of available studies.

1. Screen preoperatively for psychological problems such as anxiety, depression, and stress, and identify those patients for special attention, especially if they are having a high-risk procedure
2. Control preoperative pain aggressively.
3. Consider the perioperative use of gabapentin or pregabalin or ketamine.
4. Use epidural analgesia for thoracotomy and major laparotomy and paravertebral blockade for breast surgery.
5. If regional anaesthesia is not practical, consider perioperative intravenous lidocaine infusion.
6. Control immediate postoperative pain aggressively and for as long as necessary by any appropriate means.

Adapted with permission from reference [125].

Table 1. Evidence-based strategies to reduce the risk of chronic post-surgical pain (CPSP).

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