CHAPTER 2

LITERATURE REVIEW

2.1 Literature search strategy

The literature search strategy used to locate the information in this review is the MEDLINE reference database and additionally by going through the reference lists of other articles. The keywords used were pre-emptive analgesia, preincisional morphine and postoperative pain. The year covered by the search was from 1985-1996.

2.2 Pain mechanism

Normally, pain is felt when impulses reach a conscious brain along fine myelinated (Aδ) and/or unmyelinated (C) nociceptive nerve fibers. The sensory endings of these afferent fibers are normally activated only by strong, noxious stimuli, and the brain interprets input arriving along them as being painful. This matchup between the high threshold of the

afferent endings in the periphery and their corresponding central connections makes the pain system as effective sensory signaling apparatus.

The pain we experience in our everyday lives when exposed to noxious stimuli is defined as physiologic pain. Physiologic pain is qualitatively different from the clinical pain experienced after frank tissue or nerve injury has occurred[8]. Physiologic pain has a high threshold, is well-localized and transient, and has a stimulus-response relationship similar to that of other somatosensations. Its fundamental role is to operate as a protective system, warning of contact with potentially damaging stimuli. The stimuli required to elicit this pain are sufficiently different from those that produce innocuous sensations that we can reliably predict whether a given stimulus is likely to produce pain or not. This is due to the highly specialized peripheral sensory pathways that subserve these different sensations: the large Aβ primary sensory fibers for innocuous and the fine Aδ and C fibers for noxious stimuli.

Clinical pain can be divided into inflammatory and neuropathic pain. Inflammatory pain refers to pain associated with peripheral tissue damage, whereas the neuropathic pain refers to damage to the nervous

system. Both are characterized by changes in sensitivity, notably a reduction in the intensity of stimuli necessary to initiate pain so that stimuli that would never normally produce pain begin to do so (allodynia). There is also an exaggerated responsiveness to noxious stimuli (hyperalgesia) and a spread of hypersensitivity to noninjured tissue (secondary hyperalgesia).[8] Two mechanisms operate to produce these changes in sensitivity found in inflammatory pain. The first is "peripheral sensitization". Here, tissue trauma, infection, etc., cause nociceptor endings to become hypersensitive. The result is that weak, previously non-noxious stimuli now become active nociceptors and elicit pain. The tenderness of peripheral sensitization is thought to be induced by inflammatory mediators such as bradykinin and prostaglandins. Preventing peripheral sensitization has been assumed to be the major action of non-steroidal anti-inflammatory drugs (NSAIDs) by virtue of the inhibition of prostaglandin production by the inhibition of the enzyme cyclooxygenase.[9] The second mechanism is a change in the excitability of neurons in the spinal cord, triggered by nociceptive afferent inputs. This is the phenomenon of "central sensitization". By modifying the response properties of central neurons, central sensitization is responsible for at least some of the changes in mechanical

sensitivity that occur at the site of an injury and all the changes in the zone of secondary hyperalgesia outside the sites of injury. The fundamental difference between peripheral and central sensitization is that the former enables low-intensity stimuli to produce pain by activating sensitized Aδ and C nociceptors, whereas the latter represents an input in normal low-threshold Aβ sensory fibers producing pain as a result of amplification in sensory processing in the spinal cord. This noxious input-triggered form of central sensitization appears to involve the activation of n-methyl d-aspartate (NMDA) receptors and hence might ultimately be brought under control using NMDA receptor antagonists.

2.3 Pre-emptive analgesia and treatment of post-operative pain

We have known about the peripheral sensitization caused by surgical and non-surgical injury and inflammation for a very long time. Postoperative pain is certainly triggered when peripherally sensitized nociceptors are activated by the weak stimuli present when a patient is at rest or moving. Appropriately, this classical mechanism has been integrated into the routine of analgesic treatment in the postoperative

period. This is the role of anti-inflammatory agents, corticosteroids and particularly NSAIDs. The identification of secondary hyperalgesia and central sensitization as a second contributing mechanism[8] has opened an equally important new window of opportunity for pain control. First, it might be possible to counter central sensitization directly in the same way that NSAIDs counter peripheral sensitization.[9] NMDA-receptor antagonists might be a possible novel family of analgesic drugs used as the direct pharmacological approach. Pre-emptive analgesia is a second such approach.

A natural conclusion is that one might be able to attenuate postoperative pain and avoid the need for drugs that counter central sensitization simply by blocking or attenuating the surgically-induced nociceptor barrage.[4,5] This would prevent the development of central sensitization and pre-empt the postoperative pain caused by it. Regional analgesia or systemic analgesia (e.g. opiates) as a supplement to general anesthesia before the first surgical incision is made may be the answer to this.

2.4 Clinical studies

Since the idea of pre-emptive analgesia had been advocated, there were several clinical studies carried out to support this idea. Those studies are grouped as follows:

2.4.1 Comparison of the effect of pre- versus postsurgical local anesthetic blockade on postoperative pain.

Ringrose et al. used femoral-nerve block in patients undergoing knee-joint surgery under general anesthesia with nitrous oxide and fentanyl.[10] The patients who had pre-emptive block received less opiate analgesia postoperatively. However, the study was not run blind and the evaluation of how much opiate to give was "at the discretion of the nursing staff". Two other studies with similar protocols[11,12] obtained contradictory results.

Turner and Chalkiadis tested lidocaine infiltration of the surgical wound site pre- and postsurgical appendectomy.[13] They did not find any difference in postoperative pethidine requirement in the two groups.

Another study, performed under general anesthesia and opioids, compared the effect of bupivacaine subcutaneous infiltration before and after abdominal hysterectomy.[14] There was no difference between groups.

The effect of local anesthetic infiltration was also tested in patients undergoing tonsillectomy under general anesthesia.[15,16] In a trial of pre-tonsillectomy infiltration versus no infiltration, they found a favourable effect of the local anesthetic.[15] Another study using pre- versus post-tonsillectomy infiltration, showed no difference in post-operative pain between the two groups and no evidence of pre-emptive analgesic effect.[16]

2.4.2 Pre- versus postsurgery epidural analgesia using local anesthetics.

Three studies examined the effect of caudal epidural block with local anesthetics in children undergoing ambulatory operation under anesthesia..[17-19] There was no significant difference in pain or use of analgesics postoperatively between those who received the caudal block

before versus at the end of surgery. Three other studies tested the effect of pre- versus postsurgical treatment in adults undergoing lower abdominal operation.[20-22] All studies were performed under general anesthesia using nitrous oxide and a gas anesthetic. In two of the studies,[20,21] the use of epidural local anesthetics before surgery significantly reduced postoperative pain and analgesic requests compared to the groups given the same drugs at the end of surgery. In the third study,[22] however, no such effect was observed.

2.4.3 Pre- versus postsurgery epidural analgesia using local anesthetics and opioids.

In two separate studies using epidural morphine in addition to bupivacaine, Dahl et al. did not find a significant difference in post-operative pain or requests for additional analgesics in patients who underwent major abdominal surgery or total knee arthroplasty.[23,24]

2.4.4 Pre- versus postsurgery epidural analgesia using opioids.

Katz et al. gave epidural fentanyl either prior to thoracotomy or 15 minutes after the incision.[25] The group with pre-emptive treatment had significantly reduced pain intensity (visual analog scale -VAS) 6 hours postoperatively. At 12-24 hours the pain scores were equal, but only because of the larger amounts of morphine drawn from the patient-controlled analgesia (PCA) units by the group that received fentanyl postincisionally.

2.4.5 Pre- versus postsurgery systemic opioids.

Richmond et al. reported that intravenous morphine given before versus just after surgery for abdominal hysterectomy yielded a 27% reduction in the consumption of opiates during the first 24 hours postoperatively and a reduction in the tenderness of skin near the scar[26] This experimental design was later repeated by Collis et al, using a higher dose of morphine.[27] Slightly better analgesia was obtained, but an unacceptable level of nausea was noted. These positive results encouraged additional studies on abdominal hysterectomy using other opioids.[28,29] Unfortunately, neither found a significant difference that would have indicated the presence of pre-emptive analgesia.

In conclusion, the existing clinical studies do not consistently demonstrate the benefits of pre-emptive analgesia. Even the trials that showed the most prominent effect of pre-emptive analgesia[26,27] were not perfect. These two studies scrupulously avoided the use of pre-operative opiates in the postincisional group, whereas routine anesthetic practice almost always includes supplemental analgesics. Moreover, the timing of morphine administration in postsurgical group was a little later than what we usually do in current practice and the adverse effects of morphine given at wound closure had not been mentioned.