# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Literature search strategy

The MEDLINE reference database was searched for the information in this review by using the keywords: patient-controlled epidural analgesia, ropivacaine, bupivacaine, total knee arthroplasty, total knee replacement and postoperative pain and limited the search to English language from year 1980-2002. And also, the information from the references lists of those articles were extracted.

## 2.2 Patient- controlled epidural analgesia

The management of postoperative pain can be improved with the use of epidural analgesia. Postoperative epidural analgesia is mostly provided by continuous infusion or patient controlled analgesia (PCA). Patient controlled analgesia allows patient to self titrate at the desired level of analgesia. Silvasti and Pitkanen[11] found that the amount of the solution consumed is significantly less with patient controlled epidural analgesia (PCEA) than with continuous infusion for postoperative analgesia after total knee arthroplasty. Some investigators found that providing analgesia with patient controlled epidural analgesia (PCEA) may improve analgesia , patient satisfaction and safety compared with continuous epidural infusion. It was suggested that psychological or pharmacological mechanism may be responsible for this

difference. Reduction in anxiety and having sense of control may have increased the placebo effect of PCEA. In addition, intermittent bolus administrations with PCEA technique may have allowed more contact of drugs to receptors and more effective CSF penetration of local anesthetic and opioid than a continuous infusion[12].

**2.3 Local anesthetics and opioids**

Many pharmacologic agents have been used for epidural pain management however conventional agents include local anesthetics or opioids are commonly used either single agent or the combination. If local anesthetic is used alone, to provide sufficient pain relief may cause motor block yielding discomfort or difficult with ambulation or hypotension. This untoward effects are related to type, concentration, or volume of local anesthetic agent. Lidocaine which is one of the older local anesthetics has less level of motor sensory seperation and shorter duration compared to bupivacaine. Therefore, lidocaine is not commonly used for pain management of the postoperative patients while bupivacaine has been traditionally used as local anesthetic of choice. On the other hand, epidural opioid analgesia at the clinical dose can provide good pain control at rest but often inadequate during activity. If dose of opioid is increased, it will result in an increase in the incidence of side effects such as pruritus, nausea, vomiting and respiratory depression. Considering of the site of actions of local anesthetics and opioids which are at the different sites, using the combination of these two agents theoretically will result in additive or synergistic effect. Morphine and fentanyl are the most two opiods which have been used for postoperative pain therapy either by continuous or by patient controlled epidural analgesic methods. However, fentanyl is more preferable due to its rapid onset, easy

titration, and less side effects. Two experimental studies[13-14] and many clinical studies[15-16] have confirmed the synergism between local anesthetics and opioids. However the additive or synergistic effect of fentanyl and bupivacaine may depend on the optimal ratio of these two agents. Badner[17]did not demonstrated the additive effect of low dose bupivacaine (0.1%) to fentanyl for epidural analgesia. In that study, the ratio of bupivacaine to fentanyl was 1 mg :10 μg (1:10) instead of 1:5 or 1:4 as stated by Cooper[15] for being the optimal ratio. Cooper suggested that the relatively large dose of fentanyl used in Badner's study may have masked any beneficial effect of the additive of bupivacaine to fentanyl. In clinical practice, a combination of local anesthetics and opioids is used to take advantage of synergy between these two agents. By using this combination, the amount of each agent is reduced leading to a better effect profile. Nevertheless opioid related side effects are still troubling to some patients or practitioners.

Recently, ropivacaine[18], a new long acting amino-amide local anesthetic has been introduced into clinical practice. In extensive pharmacokinetics and pharmacodynamics studies of ropivacaine both in animals and human volunteers supports the concept of a lower potential for systemic toxic effects of ropivacaine compared with bupivacaine [19-22]. Additional advantages of ropivacaine include better motor sensory separation at lower concentration than bupivacaine [23]. These properties seem to make ropivacaine an ideal agent for postoperative pain control.

**2.4 Clinical studies**

Epidural analgesia with 0.2% ropivacaine which is the manufacturer's

recommended concentration for postoperative analgesia, has been studied for its analgesic action and side effects. Turner[24] and Etches[25] found that with 0.2% concentration, at a rate of 8 ml/h or more is required to provide good analgesia for continuous epidural analgesia. However, infusion at this rate may associated with an increase in the incidence of motor block and urinary retention especially when epidural catheter is placed at lumbar region. Since early ambulation is one of the goals of postoperative pain management, 0.2% ropivacaine does not seem to be appropiate for continuous epidural infusion due to significant motor block. Badner et al.[26] did a randomized, double blind study comparing 0.1%, 0.2 % or 0.3 % ropivacaine by continuous epidural infusion for postoperative pain relief in total hip and knee arthroplasty. They found less motor block but more rescue analgesic drug when using 0.1% compared with 0.2% and 0.3% ropivacaine. According to these evidences and also the better motor sensory separation at lower concentration, 0.15% ropivacaine may be the suitable concentration for postoperative analgesia. Therefore, ropivacaine alone may be used for postoperative analgesia in case of great concern of opioid related side effects.

To date, 0.0625% bupivacaine in combination with 3-5 mcg/ml of fentanyl has been suggested for postoperative epidural analgesia [27]. Since ropivacaine which has some properties superior to bupivacaine not only safety profiles but also its selectively differential sensory block, using 0.15% ropivacaine as a single agent for postoperative pain control seems to be a promising agent with the advantages of the avoidance of opioid related side effects and will be an alternative to the combination of local anesthetic and opioid in patient who is at risk to opioid. In addition, up to now there is no randomized controlled trials comparing between these two regimens as PCEA

technique. Therefore, by using PCEA with 0.0625% bupivacaine plus fentanyl compared to 0.15 % ropivacaine after total knee replacement is a subject of our interest. Since post TKR surgery produces a very strong pain and PCA allow patient to titrate analgesic to their own individual requirement, to do a comparative analgesic study in this clinical setting is deemed to be a valid model.

**2.5 Conceptual framework**