The Safety and Efficacy of Liposomal Bupivacaine Administration in Patients Undergoing Shoulder Arthroplasty: An Integrative Review

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Abstract

The aim of this integrative review is to examine and report current evidence regarding the safety and efficacy of liposomal bupivacaine (LB) administration for post-operative analgesia in shoulder arthroplasty. The two administration methods examined are peri-neural and peri-articular infiltration. Articles published between 2008 and 2018 were critically appraised for validity, reliability, and rigor of study.

The safety profile of subcutaneous and peri-neural administration of LB has been well documented by research. Risks of myotoxicity and neurotoxicity from LB administration are similar compared to Bupivacaine HCL when used at lower dosages (2.5-3 mg/kg). Evidence from animal studies show that peri-articular infiltration of LB introduces less risk of chondrocyte death compared to Bupivacaine HCL.

Peri-articular infiltration of LB is most efficacious when combined with a single shot interscalene nerve block (ISNB) containing Bupivacaine or Ropivacaine HCL. If ISNB is contraindicated, peri-articular infiltration of LB should be combined with Bupivacaine HCL to provide earlier onset local anesthesia. More research is needed to determine which method of LB administration is more effective in reducing post-operative pain scores and narcotic usage; intra-articular infiltration or interscalene nerve blockade. The current published research does not provide enough evidence to suggest that administration of LB via single shot ISNB provides better pain relief compared to peri-articular infiltration. If ISNB is preferred, it is suggested LB be co-administered with Bupivacaine HCL. More research is needed to determine which method of LB administration is more efficacious; peri-articular infiltration or interscalene nerve blockade.

Introduction

Total shoulder arthroplasty (TSA) is one of the most commonly performed elective procedures in the elderly population with greater than 50,000 per year.[1,2] Considering this growth, increasing the incidence of successful ambulatory TSA could result in lower healthcare costs. Ambulatory TSA costs an average of $3,614 less compared to inpatient TSA.[2]

An important aspect of outpatient surgery is post-operative pain management and prevention of complications. Opioid use is associated with respiratory depression, somnolence, increased time to mobilization, constipation, and increased time to discharge.[3] In addition to the risk of adverse effects there is also increased risk of persistent opioid use well after the surgical recovery period. Research has shown that 5.9-6.5% of surgical patients continue to use opioids more than 90 days after having surgery. To put this into perspective, in 2010 over 50 million ambulatory surgical procedures were performed. Based on this study's findings, this means that 2 million surgical patients developed a new opioid dependence.[4]

There are several modalities and techniques to manage pain and reduce narcotic consumption after TSA; however, the interscalene nerve block (ISNB) is considered the "gold standard" for shoulder analgesia. Successful ISNB can provide ideal analgesia for surgical conditions in addition to providing adequate pain control in the immediate post-operative period. However, patients receiving ISNB often experience rebound pain when the block wears off 8-10 hours post-operatively.[5,6] Because of this, patients often require intravenous doses of opioids to alleviate the pain, even in the presence of multi-modal pain regimens consisting of NSAIDs and GABA analogues.[6]

In an attempt to extend the effects of local anesthesia, different methods of local anesthetic administration have been introduced. Indwelling interscalene catheters allow

continued delivery of local anesthetic to provide longer analgesia compared to a single shot ISNB. However, several studies have demonstrated indwelling catheters increase costs and complications.[3,7-9] In April 2018, liposomal bupivacaine (LB) was approved for use in ISNB by the Food and Drug Administration (FDA).[10] This presents an opportunity for anesthetists to extend the duration of action of ISNBs while avoiding the costs and complications associated with indwelling catheters.

There are two methods to administer LB to provide shoulder analgesia; peri-articular infiltration and perineural infiltration (peripheral nerve blockade). Peri-articular infiltration of LB has been an approved indication by the FDA since 2011.[13] However, there is limited research comparing effects of interscalene and peri-articular LB infiltration.

Aims

The aim of this integrative review is to examine and report current, evidence-based recommendations regarding the use of LB for post-surgical analgesia after shoulder procedures; specifically regarding peri-articular infiltration and perineural infiltration via interscalene nerve block. The questions that guide this review are as follows:

1. Is interscalene and/or peri-articular LB infiltration safe for the patient in terms of cardio, neuro, and myotoxicity?
2. How does interscalene and/or peri-articular LB infiltration affect narcotic consumption, pain scores, and hospital length of stay (LOS)?

Methods

A literature review was conducted using the library database system at Bryan College of Health Sciences. CINAHL, SCOPUS, PUBMED/MEDLINE Complete, and Google Scholar were the databases used. The following keywords were searched alone and in combination:

Exparel, liposomal bupivacaine, shoulder, pain, intra-articular, peri-articular, brachial plexus, and interscalene. The literature search was limited to English-language articles published between 2008 and 2018. A matrix was used for data extraction and categorizing references and findings.

Results

Liposomal Bupivacaine: A Review

Currently there is only one formulation of LB approved for use in humans in the United States. Its brand name is Exparel; owned by Pacira Pharmaceuticals. LB consists of spherical, multivesicular liposomes that are organized in a honeycomb-like structure. Each liposome has an aqueous chamber containing bupivacaine free-base in the concentration of 1.33%. Each aqueous chamber is separated from the next by phospholipid membranes.[11]

Body heat destabilizes the phospholipid bilayers, which causes the membrane to degrade, releasing the bupivacaine free-base contained inside. This results in a slow release of the local anesthetic, typically over 72-96 hours. Plasma concentration of this liposomal formulation peaks between 24 and 48 hours in comparison to bupivacaine hydrochloride (HCl) whose plasma concentrations peak at 30 to 40 minutes.[12]

LB belongs to the amide class of local anesthetics, meaning that this type of local anesthetic has an amide linkage between its lipophilic group (benzene ring) and its hydrophilic group (tertiary amine). Its mechanism of action is by blocking intra-cellular sodium ion channels of nerves. Blocking these channels results in an increased threshold for electrical excitation in the nerve, thereby reducing the rate of pain signal transmission to the brain.[11]

According to the Exparel (LB) package insert, non-bupivacaine local anesthetics should not be combined with LB in a single administration. This can cause immediate and rapid release

of bupivacaine from the liposomes, resulting in dangerously high concentrations of bupivacaine free-base. However, LB can be safely combined with bupivacaine HCl without disrupting the integrity of the liposomes. LB may also be diluted with isotonic solutions like normal saline however, dilution with any hypotonic solutions will result in disruption of the phospholipid membranes of the liposomes.[13]

Safety

Cardiotoxic Profile of Liposomal Bupivacaine. The cardiotoxicity of bupivacaine HCl and its effects on the QT/QTc interval is well established in the anesthesia literature. Bupivacaine is a known sodium channel blocker, but it has also been shown to block potassium and calcium channels. This leads to a prolonged action potential and risk for arrhythmias.[14] LB is administered in a 1.33% concentration compared to the typical 0.25-0.5% bupivacaine HCl concentration. With this increase in concentration, it is important to determine if there are increased cardiotoxic effects.

Two studies were conducted to determine if LB induced more cardiotoxic effects compared to bupivacaine HCl. In one study, researchers administered LB subcutaneously in healthy volunteers. They found that even in dosages much higher than the recommended dose (750 mg vs. 266 mg), there was no QTc value greater than 500 milliseconds (ms) or any increase of QTc greater than 60 ms. These results were not statistically significant.[14]

In the second study, researchers administered 266 mg of LB via interscalene block or intercostal nerve block in surgical patients, then performed Holter monitoring for 72 hours. They found that both recorded and self-reported tachycardias were as frequent in the placebo (normal saline) group as the LB peripheral nerve block group. Cardiac events such as high-grade blocks, bradyarrythmias, ventricular tachycardia, supraventricular tachycardia, and atrial fibrillation

were uncommon and evenly observed among LB and placebo patients. Unfortunately, researchers did not provide any statistical information regarding significance making it difficult to determine the clinical relevance of this information.[10] It is worth noting that both of these studies were supported financially by Pacira Pharmaceuticals, the owner of Exparel, creating a risk of bias that must be considered.

LB may have a more favorable cardiac safety profile compared to bupivacaine HCL. This is important because inadvertent intravascular injection is a risk associated with peripheral nerve block administration, leading to potential cardiotoxicity. A study conducted on animals showed that intravascular LB maximum dosages at which no meaningful adverse events were observed were much higher than for bupivacaine HCl. Bupivacaine HCL administered intravenously at 1.8 mg/kg and intra-arterial at 0.1 mg/kg elicited symptoms of toxicity such as tachycardia, hypertension, labored breathing, tremors, and convulsions. The maximum dose of LB at which there were no adverse effects was 4.5mg/kg administered both intra-arterial and intravenous. This study suggests that LB may have a more favorable cardiac safety profile compared to bupivacaine HCl. The weaknesses of this study include the small sample size (N=5), the information gathered is on animal subjects and the researchers involved in the study are supported financially by Pacira Pharmaceuticals.[15]

Neurotoxic and Myotoxic Profile of Peri-neural Liposomal Bupivacaine.

Administration of high concentrations of local anesthetic can induce neurotoxic and myotoxic reactions to surrounding tissues such as decreased nerve fiber density and inflammation of muscle tissue. Three studies were found examining the neurotoxic and myotoxic effects of perineural LB administration compared to bupivacaine HCl. The research demonstrated that LB administered in sciatic and brachial plexus blocks at a dose of 25 mg/kg showed neurotoxic or

myotoxic effects.[16,17] However, there was a significantly higher amount of inflammation compared to tissue infiltrated with 0.5% bupivacaine HCl, indicative of myotoxicity ($p = 0.006$).[17] When LB was administered at 2.5-3 mg/kg, which is a much more typical dose administered to human subjects, the research showed no differences in inflammation ($p = 0.135$), in addition to no significant changes in nerve fiber density ($p = 0.214$), or myelin width ($p = 0.990$), indicative of nerve injury between LB and placebo.[18]

Chondrotoxic Profile of Peri-Articular Liposomal Bupivacaine. Chondrocyte death is a known result of exposure of articular cartilage to local anesthetics, especially after intra-articular infusion pumps for shoulder and knee procedures. One study was found that examined the chondrotoxic profile of LB. Researchers compared chondrocyte viability in pigs after intra-articular injection of bupivacaine HCl or LB. They found that there was significantly more cell death in the bupivacaine HCl group compared to the LB group ($p = <0.01$). Interestingly, researchers found that cartilage exposed to LB showed the same amount of chondrocyte death (6.2% vs. 5.8%) as the cartilage from the control group, which was not exposed to any local anesthetic.[19]

Based on the above findings, it is suggested that anesthetists are introducing as much risk to the patient by injecting LB as bupivacaine HCl. However, the weaknesses of this study should be taken into account. The sample size for the study is small ($N = 8$), this study was performed on animals, and there was no blinding.

Efficacy

Peri-articular Infiltration of Liposomal Bupivacaine. Peri-articular infiltration is an extensive, scrupulous method of administering local anesthetic (low concentration, high volume) into the surgical wound (soft tissue, ligaments, and capsule) prior to closure. The peri-articular

infiltration technique is performed in three separate phases during the surgical procedure. First the deep structures are infiltrated after preparation of the shoulder joint and after the glenoid insertion, but before the humeral component is placed (see Figure 1). Thirty mLs of solution are injected into the periosteum all around the glenoid, into the posterior capsule, anterior capsule, subscapularis muscle, and the periosteum around the humeral side (see Figure 2). Next, after the insertion of the humeral component, 30 mLs of solution are then injected into the subscapularis muscle tendon and deltoid and pectoralis muscles (see Figure 3). Lastly, 30 mLs are injected subcutaneously around the incision prior to closing (see Figure 4).[20]

Seven research studies were found that evaluated the efficacy of peri-articular infiltration with LB in patients undergoing shoulder arthroplasty. Among these studies were different combinations and modalities in using LB. These combinations and modalities will be discussed next.

Interscalene Nerve Block With and Without Peri-articular Infiltration of Liposomal Bupivacaine. The two studies comparing peri-articular infiltration in combination with single shot ISNB versus ISNB alone had conflicting results.[1, 26] Researchers from one study found the addition of peri-articular LB to single shot ISNB resulted in significantly lower pain scores 18-24 hours ($p = 0.001$) and 27-36 hours ($p = 0.029$) postoperatively. In addition, they also found significantly lower narcotic requirements on postoperative days 2 ($p = 0.001$) and 3 ($p = 0.002$).[1] Researchers from the second study found there was no significant difference in postoperative pain scores during the first 72 hours after surgery. Additionally, during the first 24 hours post-op there was significantly higher narcotic consumption in the patients that received both peri-articular LB and ISNB ($p = 0.009$).[26] Considering this information, one cannot conclude whether

the addition of LB to single shot ISNB is beneficial in decreasing postoperative pain scores and/or narcotic consumption in patients undergoing shoulder arthroplasty.

Indwelling Interscalene Catheters Compared to Peri-articular Infiltration of Liposomal Bupivacaine With or Without Single Shot Interscalene Nerve block. Two studies were found comparing the effects of indwelling interscalene catheters and peri-articular infiltration of LB. In patients undergoing shoulder arthroplasty, it was found that peri-articular infiltration of LB in combination with single-shot ISNB had equivalent narcotic use, pain scores, and time to first narcotic rescue ($p = >0.05$) compared to patients who received an indwelling interscalene catheter. It was also found that the infiltration of LB in addition to single-shot ISNB resulted in less cost ($300 savings) and rate of complications (5.9% vs 19.4%) compared to indwelling interscalene catheters.[3]

However, peri-articular infiltration of LB in the absence of a pre-operative single shot ISNB resulted in significantly higher pain scores and opioid consumption in the first 24 hours after surgery compared to indwelling interscalene catheters ($p = <0.05$). After the first 24 hours and for the remainder of the admission there were not statistically significant differences in pain scores between the two groups, this is possibly due to the delayed onset of action of the LB.[7]

When considering the information provided by the two research studies above, one can say that it is plausible peri-articular infiltration of LB can provide similar pain relief to indwelling interscalene catheters, while decreasing costs and risks of complications associated with indwelling nerve catheters. However, due to the delayed onset of action, peri-articular infiltration of LB must be performed in combination with a single shot ISNB to provide adequate pain relief in the immediate postoperative period. Further research will be needed to make this statement with more certainty.

*Peri-articular Infiltration of Liposomal Bupivacaine Compared to Single Shot Interscalene Nerve Block***.** Three studies were found comparing peri-articular infiltration of LB alone versus a single shot ISNB. The research showed that when compared to single-shot ISNB, peri-articular infiltration of LB alone does not decrease opioid consumption, reported pain levels, or length of stay.[5,21,22] Patients who did not receive a pre-operative ISNB had significantly higher intra-operative narcotic requirements ($p = <0.05$) and increased pain scores during the first eight hours postoperatively ($p = 0.001$).[5] However, when peri-articular infiltration of LB was combined with bupivacaine HCl, there were no significant differences in pain scores during the first 12 hours post-operatively compared to patients that received a single shot ISNB. These results can be attributed to the earlier onset of action of the bupivacaine HCl providing local analgesia during the time that the LB is not yet effective.[22] It is also worth noting that in studies where patients were administered a single-ISNB without peri-articular infiltration of LB, rebound pain and increased opioid requirements were present when the ISNB wore off.[1,5,21]

There were several limitations in the seven studies mentioned above. All of the studies had small sample sizes ranging from 57-78 participants and some studies only measured pain scores and opioid consumption 24 hours post operatively. This could potentially have an effect on pain sensation post operatively. Additionally, due to ethical reasons, none of the studies had control groups where participants did not receive either ISNB or local infiltration of local anesthetic. Two of the studies also used other non-opioid anesthetics such as NSAIDs and/or intravenous acetaminophen post operatively.[1,3] Lastly, due to the nature of the studies, there was no blinding of the surgeons or anesthetists administering the local anesthetic via ISNB or local infiltration.

Peri-neural Infiltration of Liposomal Bupivacaine. There is very limited research available regarding the pain relieving effect of LB when administered via peri-neural infiltration (peripheral nerve block). While researching LB infiltration in brachial plexus nerve blocks, 5 studies were found; 3 studies evaluating post-surgical pain in hand/wrist surgeries and 2 studies evaluating pain after shoulder surgery. Only the two studies evaluating pain after shoulder surgery will be discussed, as they are the most pertinent to the aim of this integrative review.

The two studies that evaluated LB administration via ISNB for shoulder surgery both found that LB resulted in significantly lower pain scores. One of the studies found a significant decrease in opioid consumption compared to placebo ($p = <0.001$) and the other study did not find any difference in opioid consumption compared to ISNB containing only bupivacaine HCl ($p = >0.05$).[10,25]

The two studies mentioned above had several weaknesses. Both studies were funded by Pacira Pharmaceuticals, the owner of Exparel (brand name for LB). This introduces a risk of bias that must be considered when evaluating the results of these studies. One of the studies compared ISNB containing LB to ISNB only containing normal saline.[10] While it is considered a strength to have a negative control group in a research study, it is not standard practice to use only normal saline in a ISNB. The findings of this study would be more pertinent if compared to ISNB containing bupivacaine HCl as this is a more typical administration for regional shoulder analgesia. The study comparing the addition of LB to ISNB containing bupivacaine HCl had a small sample size ($N = 52$) and also administered other non-opioid analgesics such as Decadron and Toradol.[25]

Discussion

This integrative review indicates a trend towards increased use of longer acting local anesthetics such as LB in place of indwelling interscalene catheters in total shoulder arthroplasty.[1, 3, 5, 7-8, 10, 20-22, 24-26] Specific anesthetic recommendations for practice that serve as starting points for integration into using LB in total shoulder arthroplasty have been developed using the guiding questions for this review and are discussed here.

Is interscalene and/or peri-articular LB infiltration safe for the patient in terms of cardio, neuro, and myotoxicity?

The safety profile of subcutaneous and peri-neural administration of LB has been well documented by research. Compared to bupivacaine HCL, administration of LB has similar risks of cardiotoxicity and risk of arrhythmias. [10, 14, 21] LB has increased risk of tissue inflammation, indicative of myotoxicity, when used in high dosages (25 mg/kg). However, there is similar risk compared to Bupivacaine HCL when used at lower dosages (2.5-3 mg/kg).[16-18] Evidence from animal studies suggests that there is decreased risk for chondrocyte death with intra-articular administration of LB compared to bupivacaine HCL.[19]

How does interscalene and/or peri-articular LB infiltration affect narcotic consumption, pain scores, and hospital length of stay?

Based on the research findings, peri-articular infiltration of LB alone does not provide adequate analgesia intra-operatively or immediately post-operatively. This is likely due to the delayed onset of action.[5,21] Peri-articular infiltration of LB has shown best results when combined with a single shot ISNB with bupivacaine or ropivacaine HCL.[3] It is possible that patients undergoing shoulder arthroplasty may have comorbid conditions that preclude them from receiving a single shot ISNB due to the risk of diaphragmatic hemiparesis from phrenic

nerve blockade. In this case, it is suggested that due to the delayed onset of action, peri-articular LB should be combined with bupivacaine HCL to provide earlier onset of local anesthesia. According to the medication package insert, LB can only be combined in the same administration with bupivacaine HCL. Co-administration with other local anesthetics such as lidocaine can cause immediate release of free base bupivacaine from the liposomes, resulting in toxicity.[13]

The current published research does not provide enough evidence at this time to suggest that administration of LB in a single shot ISNB provides better pain relief compared to peri-articular infiltration. [10,25] If the anesthetist and/or surgeon prefers ISNB, it is suggested that the LB be combined with bupivacaine HCL to provide local anesthesia until the LB reaches its onset of action. As mentioned above, LB can only be co-administered with bupivacaine HCL due to the risk of immediate release of free base bupivacaine when administered with other local anesthetics.[13]

Synthesis Summary Statement

The increased pain that patients experience 8-10 hours post-operatively after shoulder arthroplasty is attributed to rebound pain from the resolution of interscalene nerve blockade. This pain often requires intravenous opioid treatement.[5,6,21] The prolonged duration of action of LB presents an opportunity for anesthetists to extend the duration of regional anesthesia and further decrease narcotic requirements and shorten hospital length of stay. This could lead to improved patient satisfaction and cost savings to surgical facilities.

Limitations of this review include low strength research on analgesic strategies for shoulder arthroplasty. More research is needed to determine which method of LB administration is more efficacious, peri-articular infiltration or interscalene nerve blockade. Currently, there are

no systematic reviews or randomized control trials evaluating the effects of LB administration in ISNB compared to LB peri-articular infiltration. Additional research is also needed to evaluate the efficacy of adding LB to multi-modal pain regimens containing regional anesthesia, NSAIDs, and GABA analogues.

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APPENDIX: Peri-articular local anesthetic infiltration technique for shoulder arthroplasty

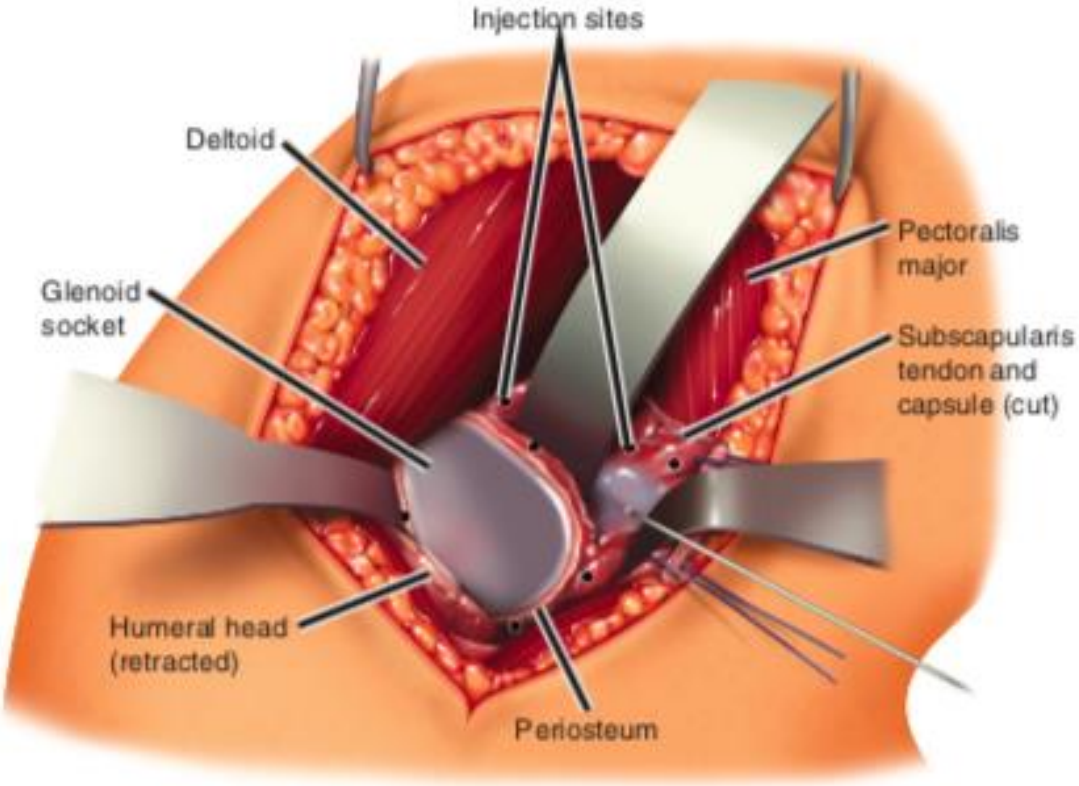

Figure 1. Deep infiltration: deep structures around the glenoid, including soft tissue and periosteum.[20]

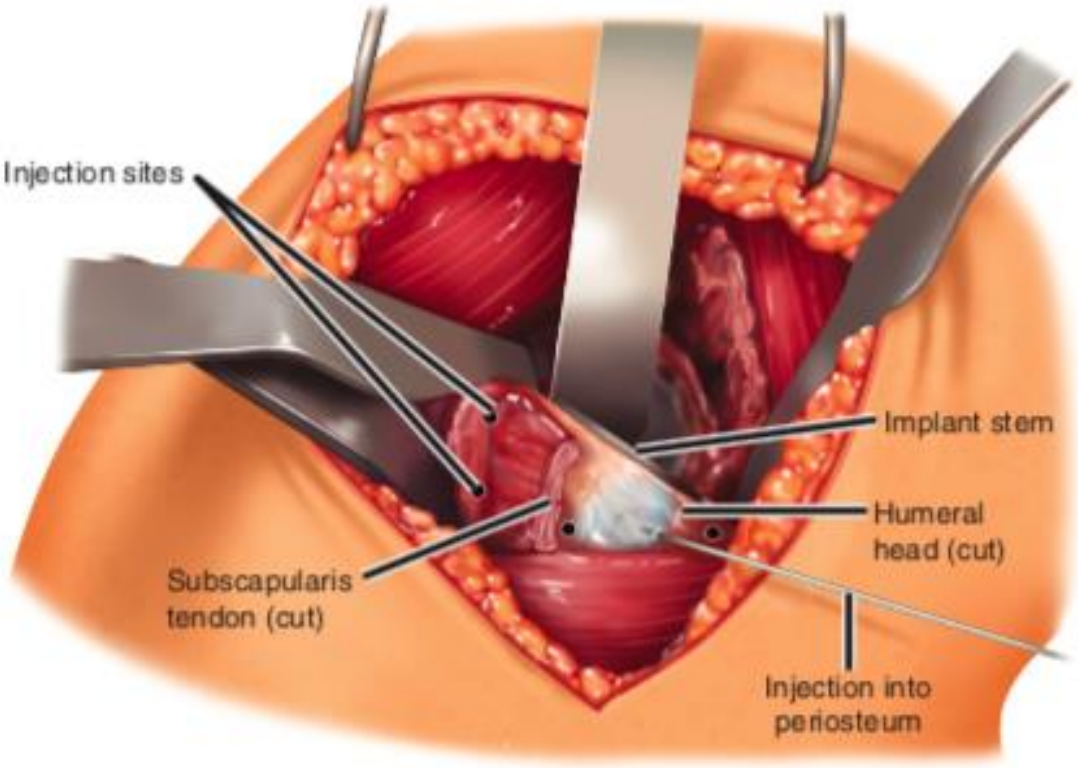

Figure 2. Deep infiltration: deep structures around the humerus, including periosteum.[20]

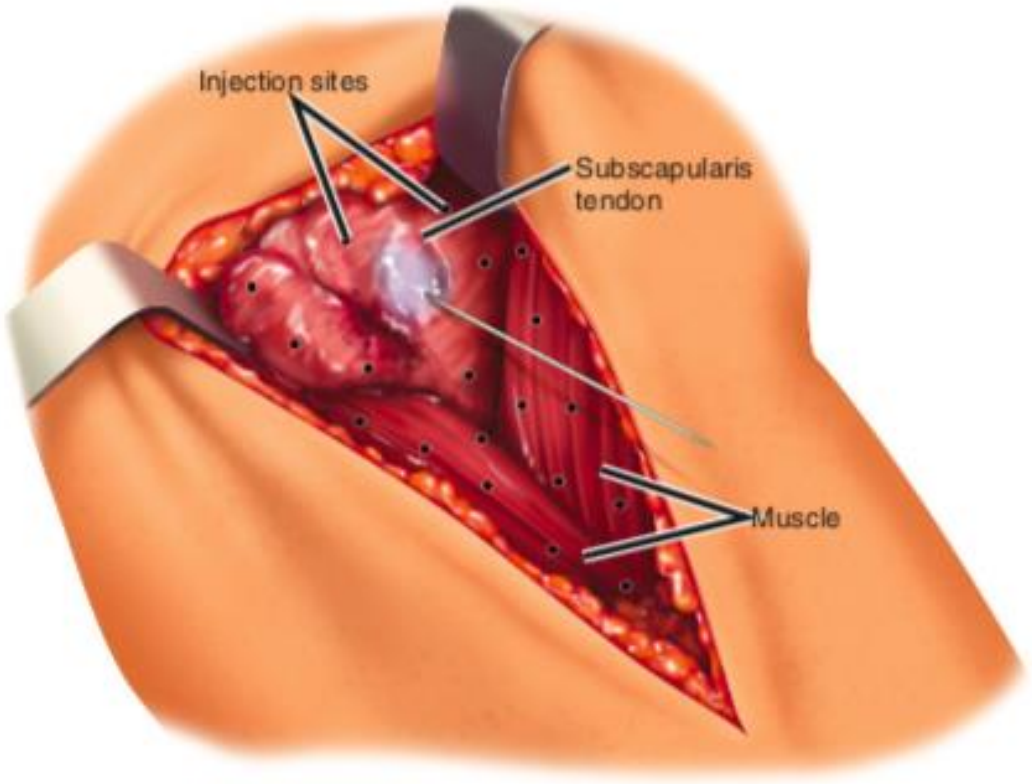

Figure 3. Midlayer infiltration: deltoid, pectoralis, subscapularis muscle, and subscapularis tendon.[20]

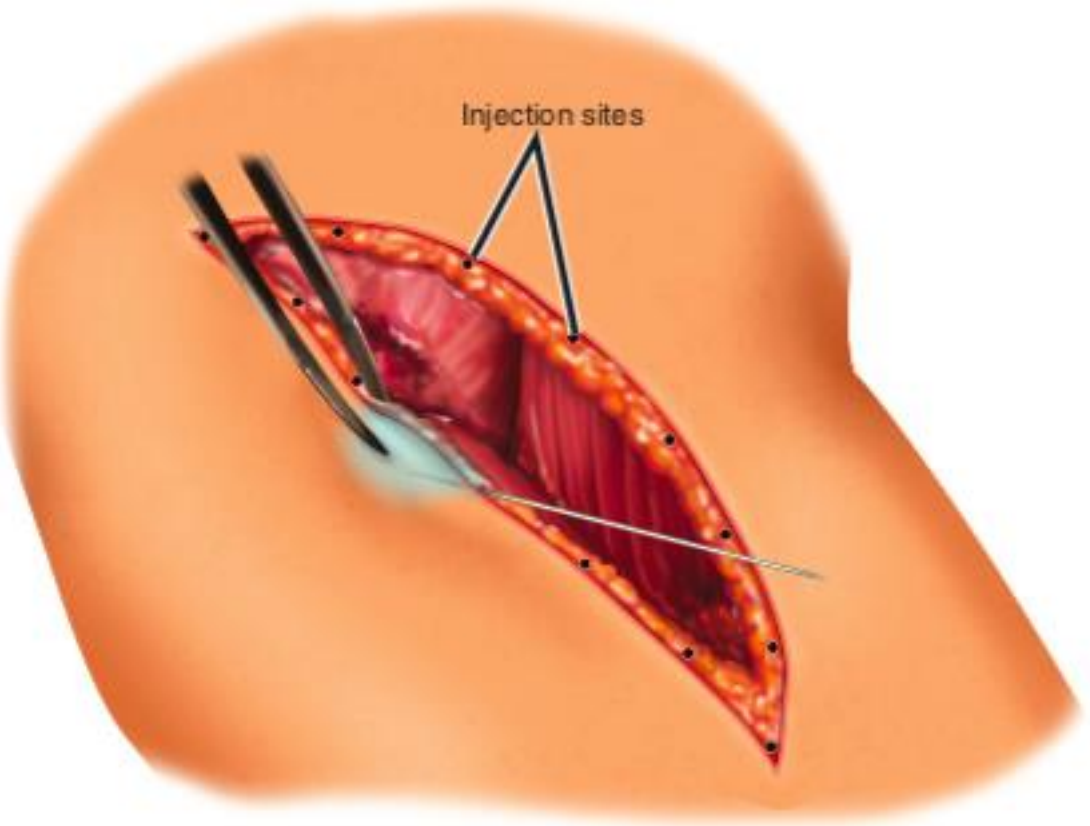

Figure 4. Superficial infiltration: subcutaneous tissue along the incision.[20]