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**ABSTRACT**

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**Introduction**

Stem cells are a group of body cells playing role in restoring damaged tissues, growing and developing body tissues [[1](#_ENREF_1)]. These cells have two main characteristics which distinguish them from another type of cells: self-renewal and differentiation potential [[2](#_ENREF_2)].

A sort of stem cells called mesenchymal stem cells (MSCs), located in connective tissues and play an important role in tissue regeneration in the injuries. These cells, which are multipotent, can differentiate into adipocyte, cartilage, bone, tendon, nerve tissue and muscle [[3](#_ENREF_3)]. This differentiation greatly depends on the niche and growth factors in the stem cells environment [[4](#_ENREF_4), [5](#_ENREF_5)]. Nowadays, the injection of stem cells has been considered for therapeutic purposes. They are used in treating some diseases such as diabetes, heart failure and diseases associated with bone marrow [[6-8](#_ENREF_6)]. Also, stem cells are used in the orthopedic field for the purposes such as repairing damaged cartilage and scrappy ligaments [[9](#_ENREF_9)]. Some substances which can be effective in the success rate of treatment are injected with the stem cells in the stem cell therapy. Anesthetics are a group of them [[10](#_ENREF_10)].

Using of local anesthetics (LA) is widely common in controlling post-operative pain and damaged tissue [[11](#_ENREF_11), [12](#_ENREF_12)]. These drugs reduce the sense of pain in patients by blocking signals. All of the local anesthetics using clinically are specific sodium channel inhibitors and prevent electrical activity in peripheral nerves [[13](#_ENREF_13)]. Local anesthetics despite benefits in reduction of pain can cause damage, too. Arrhythmias and cardiac arrest, seizures, stroke and respiratory system depression are some of these complications in some patients [[14-19](#_ENREF_14)]. Also, local anesthetics toxicity on tissues such as nerve, cartilage, muscle and tendon are well described in many studies [[20-23](#_ENREF_20)]. For example, Negative effects of bupivacaine on various cells are confirmed [[19](#_ENREF_19), [24](#_ENREF_24)].

Stem cells play a major role in regenerating damaged tissues. Local anesthetics use in operations to reduce pain widely. Investigation of effects of these drugs on stem cells helps anesthesiologists to select better LA which has lesser toxicity on repairing injuries by stem cells. LAs and Stem cells are used in some remedies, which are done with the help of stem cells, at the same time. Understanding the effects of local anesthetics on MSCs is helpful to find LAs which have lesser negative effects and to increase the success of stem cell therapy.

n this study, we have first considered the influence of local anesthetics on cells, are outcomes of differentiation of MSCs, then the effects of LA such as lidocaine, bupivacaine, ropivacaine, mepivacaine and morphine on MSCs, separately.

Anesthetics are fat soluble and can penetrate into cells and their organelles easily [[25](#_ENREF_25)]. Therefore, they can affect different tissues by influence potassium and calcium channels (in addition to sodium channels) [[26](#_ENREF_26)]. But the exact mechanism is not fully understood. Some of these cells are mentioned here:

**Materials and methods**

Local anesthetics (LA) strongly prevent glucose transport, lipolysis in fat cells and also their growth in culture. However, these effects persist only as long as they are present. After washing, the cells return to their original state and regain their growth and normal function. Local anesthetics may halt cell growth and metabolism [[27](#_ENREF_27)]. It’s noteworthy; the risks of local anesthetics are lesser than general anesthetics [[28](#_ENREF_28)].

**Bone cells**

Regional anesthetics are usually safe for bones and show a little complication [[29](#_ENREF_29)]. Although, there are some ways to form new bones, adding local anesthetics specially bupivacaine help to achieve the aim [[30](#_ENREF_30)].

**Muscle cells**

However about muscle, local anesthetics can damage muscular fibers. LAs ,including bupivacaine and lidocaine have direct cytotoxicity on myocyte [[21](#_ENREF_21)]. Bupivacaine induce releasing of Ca2+ from sarcoplasmic reticulum [SR] and prevent Ca2+ uptake by the SR, finally its intracellular level increases [[31](#_ENREF_31)].

In addition, the deranged energy balance is exacerbated by suppressing mitochondrial function. Then cell viability will be decreased. However, it seems cytotoxicity to lidocaine is minimal at a physiologic concentration in vitro [[13](#_ENREF_13)].

LAs also have adverse effects on tendons. They decrease cell viability which can be dropped by N-acetyl-L-cysteine or reduction of extracellular calcium [[32](#_ENREF_32)]. Bupivacaine for example, applies a severe reaction oxygen species-mediated effect on tendon cell viability in vitro, depending on extracellular calcium concentration [[33](#_ENREF_33)]. Anesthetics by influence on cell metabolism induce apoptosis and increase of pro-matrix metalloproteinase [[34](#_ENREF_34)]. However, these effects are impermanent [[23](#_ENREF_23)].

**Results**

About cartilage, chondrocyte viability will be decreased in contact with Las [[35](#_ENREF_35)]. Chondro-toxicity did not correlate with potency of local anesthetics [[36](#_ENREF_36)]. Bupivacaine chondro-toxicity is much more than lidocaine and ropivacaine and significantly causes fewer vital cells [[37](#_ENREF_37), [38](#_ENREF_38)]. Bupivacaine is used for the goals of infiltration, nerve block, epidural, and intrathecal anesthesia [[39](#_ENREF_39)].

Bupivacaine leads to histopathologic change and chondrotoxic effect in animal models [[40](#_ENREF_40)]. Glycosaminoglycan (GAG) accumulation/tissue volume decreases and apoptosis increases as the concentration of lidocaine increases [[41](#_ENREF_41)].

Repeated joint injection of lidocaine speed up cartilage decadence [[38](#_ENREF_38)] Its intra-articular use in any concentration in clinical process should be dissuaded. Ropivacaine may be a safer intraarticular anesthetic [[42](#_ENREF_42)].

As mentioned, LAs can reach organelles such as mitochondria, which play a vital role in cell metabolism, then lead to cell death [[43](#_ENREF_43)]. These drugs selectively decrease pro-inflammatory cytokines such as TNF-α (Tumor Necrosis Factor- α) and increase anti-inflammatory cytokines [[44](#_ENREF_44)]. After both type of cell death, necrosis or apoptosis, necrosis can occur [[38](#_ENREF_38)]. The increase in cell death is more related to cell necrosis rather than cell apoptosis [[45](#_ENREF_45)].

Preoperatively, LAs can be used both alone and in combination with other pharmaceuticals to reduce pain and narcotic character [[21](#_ENREF_21)].

A group of these pharmaceuticals are steroids such as methylprednisolone and triamcinolone which are commonly used with anesthetics in some procedures to reduce pain associated with inflammation by their anti-inflammatory effects [[44](#_ENREF_44)]. However, it has been shown the methylprednisolone has an additive toxicity with lidocaine and caution is warranted. Also, combination of triamcinolone and bupivacaine caused an intrinsic loss of chondrocyte viability but did not show a synergistic chondrocidal effects [[46-48](#_ENREF_46)].

In addition of steroid agents, there is another substance, magnesium sulfate, which can increase analgesic character and also decrease toxicity of local anesthetics, if not combination of ropivacaine and magnesium sulphate [[47](#_ENREF_47)]. It has been shown adding magnesium to LA decreases its toxicity on articular chondrocyte.

It seems location and manner of anesthetics injection have influence on potency of their effects. Maybe peri-capsular incisional injections reduce the adverse effects of LAs on articular cartilage [[49](#_ENREF_49)]. Another limitation of a study is the lack of a demonstration and identification of the absorption of anesthetics into joint tissues (i.e. articular cartilage)

At last, it is important to consider that almost all of local anesthetics are dose- and time-dependent [[36](#_ENREF_36), [50](#_ENREF_50), [51](#_ENREF_51)].

**Increase**

Necrosis and apoptosis

**Decrease**

Bupivacaine

Lidocaine

Mepivacaine

Ropivacaine

**Decrease**

1.Adhesion and cell appendages

2.Content ATP

3.Viability and function

**Increase**

**Figure 1:** Summery of effects of local anesthesia on mesenchymal stem cells

**Discussion/ Conclusion**

anesthesia’s which block pain receptors and reduce sense of pain like other members of the group. The survival rate of MSCs exposed to mepivacaine greatly depends on the concentration. Studies were designed in vitro and in the one-dimensional medium to examine the effect of mepivacaine on these cells. In these studies, the MSCs were first exposed to mepivacaine for 120 minutes. Then after 24 hours, its.

**Acknowledgement**

Local anesthetic drugs can affect almost every tissues and body cells because of their fat soluble property. Some of them include fat tissue, bone, muscle, tendon and the most important chondrocytes.

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