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Differences In Mesenkimal Stem Cell Proliferation Between Bone Marrow Type Stem Cells And Wharton's Jelly Type Stem Cells

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ABSTRACT
Various sources of stem cells in the human body, one of which is mesenchymal stem cells derived from bone marrow and Wharton's jelly. This study aims to determine differences in the proliferation count results of 2 stem cells from different sources, bone marrow and Wharton's jelly. The research was conducted using a true experimental design with in-vitro studies. Bone marrow and Wharton's jelly MSC were counted for their proliferation results at 24 hours, 48 hours, and 72 hours. The data then compared using the T-test method. The results of the study showed differences the results of the proliferation count between bone marrow and Wharton's jelly. Qualitatively, Wharton's jelly was seen in 24 hours, 48 hours, or 72 hours. However, quantitatively with statistical tests, the results that were not significant in the first 24 hours (p=0.053). At 48 hours, statistically significant results (p=0.007) were obtained because the cells began to proliferate rapidly and gave a clear difference, and at 72 hours, insignificant statistical results (p 0.074) were found because the cells were confluent and filled the substrate.The ability to reproduce is one of the characteristics possessed by stem cells. This process can be influenced by many factors so that between a culture can vary the speed of proliferation. Proliferation count showed that Wharton's jelly was more than bone marrow in 24 hours, 48 hours, or 72 hours. Different sources of MSC yield different proliferation results.

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INTRODUCTION

Regenerative medicine will be a form of health service in the future. One thing that is currently developing is stem cell biotechnology. Although stem cells are not yet standard therapy, in the future stem cell therapy is considered the final frontier of disease therapy.[1] Stem cells are biological cells found in almost all multicellular organisms that can proliferate and differentiate into various types of specialized cells and can renew themselves to produce more other stem cells.[2] Recent advances in stem cell technology have become key to therapy and patient care.[3] There is much interest in the potential use of stem cells in cell-based therapies for various human diseases.[4] Stem cell therapy plays a major role in cell transplantation. There are three basic types of transplants, namely autologous, allogeneic, and syngeneic. The type

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of transplant depends on where the stem cells come from. The ideal scientific outcome for the use of such therapy is to eradicate cancer.[5]

Stem cell research and techniques are developing rapidly and can be seen from the increasing number of scientific articles and companies and hospitals providing stem cell related products and services abroad. Various efforts have been made to develop stem cell applications, such as developing storage techniques, developing stem cell differentiation techniques towards more targeted cell types, developing techniques to increase the number of stem cells, and developing transplantation techniques.[6]

In a study regarding the number of clinical trials on stem cells using the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov before January 1 2013, there were 4749 clinical trials on stem cells. From all clinical trial data regarding the most commonly treated diseases, cardiovascular disease is in first place, neurological disease is in second place, followed by cancer and other diseases. The disease mechanisms that receive the most therapy are injuries and degenerative diseases, ischemia, and diseases resulting from the side effects of radiotherapy and chemotherapy. The types of stem cells most commonly used are hematopoietic and mesenchymal. The most widely used sources of stem cells are bone marrow, peripheral blood and umbilical cord. The increase in the number of clinical trials has increased rapidly since 2006 after the use of Mesenchymal Stem Cells (MSC).[7]

Mesenchymal Stem Cells are a type of stromal cell with specific surface antigen expression in the form of CD105(+)/CD90(+)/CD73(+), CD34(-)/CD45(-)/CD11b(-) expression and have multipotential (osteogenic) differentiation properties. , chondrogenic, and adipogenic). Clinical trial data on ClinicalTrials.gov shows 123 clinical trials using MSCs in the therapeutic field. Most were in phase 1 (safety studies), phase 2 (proof of concept for efficacy in human patients), or a mix of studies from phases 1 and 2.[8] Mesenchymal Stem Cells can be divided into two, namely adult MSCs and fetal/perinatal MSCs which originate from adult tissue, namely bone marrow (BM-MSC), adipose tissue (AD-MSC), and fetal/perinatal tissue obtained from the embryo/fetus itself. and cells obtained from extra-embryonic tissues or known as birth associated tissues such as the umbilical cord, Wharton's jelly, and amniotic membrane.[9]

For several years, MSCs have been considered a therapeutic option in regenerative medicine. Although in recent years several tissues have been described as potential sources for MSCs, human bone marrow remains one of the most studied as well as being the most widely used tissue for obtaining mesenchymal stem cell populations. The research was conducted on the influence of clinical characteristics of bone marrow donors such as age, sample condition, and volume of cells collected on the efficiency of in-vitro MSC expansion.[10]

Although the main source for MSCs is bone marrow, recently Wharton's jelly has been recognized as an excellent source for isolated MSCs. From various studies, Wharton's Jelly Stem Cell (WJSC) can differentiate into several different cell types such as osteoblasts, chondrocytes, cardiomyocytes, skeletal myoblasts, hepatocyte-like cells, endothelial cells, nerve cells, adipocytes, dopaminergic cells, and lens fiber cells. Therefore, WJSC is a cell that is multipotent, that is, it has high potential to become many cell types.[11] The difference

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between these two MSCs lies in the source of the cells themselves, bone marrow MSC which comes from the bone marrow and Wharton's jelly MSC which comes from the umbilical cord, but from comparative studies both have the same appearance and surface markers.[12]

Proliferative ability occurs when the cell cycle repeats itself without obstacles so that new cells can be formed. The cell cycle indicates cell growth that occurs during cell culture and over time. This cell growth is divided into several phases such as the lag phase which is the initial phase from planting until there is an increase in the number of cells which lasts from several hours to 48 hours, then continues with the log phase where there is an exponential increase in the number of cells and towards confluence this phase is influenced by the speed growth and cell density, then there is a plateau phase where the cells are connected to each other and cover the substrate and reach confluence so that cell growth can stop.[13]

Stem cells have the ability to proliferate so that they can form new cells, both the stem cells themselves and cells that will later be differentiated so that the formation of new tissue can occur. Stem cell proliferation has been widely studied and it has been found that what initiates the proliferation process in stem cells is the autonomic nervous system.[14] In mesenchymal stem cells, there are various things that influence proliferation itself, such as increased proliferation due to the expression of fibroblast growth factor and platelet derived growth factor-B, as well as inhibition of proliferation due to hypothermia.[15,16]

In Indonesia, health services using stem cells are regulated in the Regulation of the Minister of Health of the Republic of Indonesia Number 32 of 2018 concerning the Implementation of Stem Cell and/or Cell Services. The use of stem cells in this regulation is for standardized therapy services and research-based therapy services. This regulation also regulates general provisions, committees, services, organizers, quality audits, funding, recording and reporting, guidance and supervision, as well as provisions regarding stem cells.

Among stem cell research in Indonesia, most only focuses on one type of stem cell.[17] The difference in proliferation calculation results between types of mesenchymal stem cells according to time is very interesting to study because the ability of stem cells to proliferate more indicates one of the characteristics of stem cells, namely better self-renewal. Therefore, they can produce more similar cells that are ready to differentiate.[18] Based on the explanation above, the author is interested in comparing the differences in proliferation of the two types of stem cells before and after 48 hours as well as at 48 hours when the proliferation phase increases, both in qualitative terms or images and quantitatively with calculation results. In this case, mesenchymal stem cells, especially bone marrow stem cells as a type of adult MSC that are widely used and Wharton's Jelly stem cells as a type of perinatal MSC and have the potential to be a good source of MSC, can be tested.

METHOD

The type of research used in this research is true experimental with in-vitro studies. The research was conducted at the Biomedical Laboratory, Faculty of Medicine, Andalas University, Padang. The research was carried out from November 2019 to March 2021. The population and samples from this research were bone marrow type mesenchymal stem cells and Wharton's jelly type mesenchymal stem cells which were successfully grown in the

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Biomedical Cell Culture Laboratory, Faculty of Medicine, Andalas University. The sampling technique is based on the in-vitro cell culture method. Bone marrow mesenchymal stem cells and Wharton's jelly mesenchymal stem cells were each grown in a 6 centimeter culture dish and then incubated until 80% confluence. In each wheel there are 105 cells/mL.

The inclusion criteria are mesenchymal stem cells that look healthy and confluent, without microscopic contamination, grow and develop well. Meanwhile, the exclusion criteria are stem cells that appear to float when viewed using an inverted microscope and are contaminated with microorganisms. The variables of this study are bone marrow mesenchymal stem cells, Wharton's jelly mesenchymal stem cells, and proliferation features.

This research procedure starts from the cell thawing stage, cell planting, cell counting, and a proliferation test is carried out with a cell planting line of 105 cells in wells, then incubation of the cells is carried out, then the bone marrow and Wharton's jelly stem cells are taken into 9 dishes, respectively. then observed and counted the number of cells in the first 3 wells, second 3 wells, and third 3 wells for 24 hours, 48 hours, and 72 hours respectively, so that analysis could be carried out.

Data obtained from the proliferation test was processed using the independent sample T-test on the Statistical Program for Social Sciences computer program. To compare two samples that are not related to each other, a p value <0.05 is considered significant. The results obtained will determine which stem cells have more proliferation capacity. he research passed ethical review, research protocols, and has ethical clearance by the Ethics Committee of the Faculty of Medicine, Andalas University with letter number: 067/KEP/FK/2021.

RESULTS AND DISCUSSION

Research Data

The research was carried out using samples of two different types of MSC cells, each grown in 6-well plates and differentiated according to time. Samples obtained from the Biomedical Laboratory, Faculty of Medicine, Andalas University, Padang, were used to compare proliferation rates. This research is true experimental research using a 6-well plate with three wells for each bone marrow and Whaton's jelly Messencymal Stem Cells cell count in 24 hours, three wells for 48 hours, and three wells for 72 hours. Previously, cells were awakened or cell thawing was carried out so that new cells taken from liquid nitrogen and incubated could confluent so they could be used.

Then the cells were planted, by taking confluent cells and then cleaning the remaining medium using PBS. Because stem cells are plastic adherent cells, trypsin-EDTA is given to release the cells from the plastic base. The cells were then centrifuged then treated with Trypan Blue and viewed under a microscope. Next, dilution is carried out so that the cells can be embedded evenly into the plate. Cells were then counted on a hemocytometer using an inverted microscope. The results of each plate were photographed using a camera and the cell counting results were recorded. The difference in the proliferation results of each MSC determines which stem cell is faster in self-renewal.

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Proliferation Test Results

Table 1. Results of calculating the number of cell proliferation Punca Jenis *Bone Marrow*.

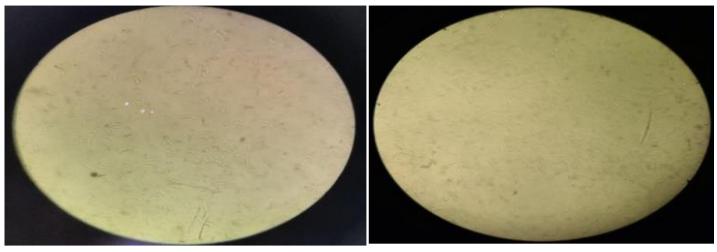
times	*Bone Marrow* (Jumlah sel/mL)		
	1	2	3
24 hours	98.000	100.000	105.000
48 hours	110.000	115.000	125.000
72 hours	130.000	145.000	160.000

Table 2. Results of calculating the number of cell proliferation Punca Jenis *Wharton's Jelly*.

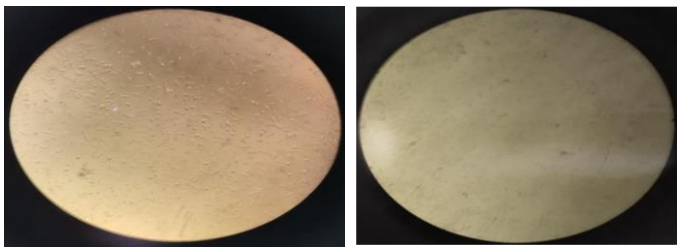
times	*Wharton's Jelly* (Jumlah sel/mL)		
	1	2	3
24 hours	110.000	115.000	130.000
48 hours	140.000	150.000	155.000
72 hours	160.000	170.000	175.000

From the proliferation test using a hemocytometer, the results obtained from bone marrow and Wharton's jelly mesenchymal stem cells were obtained. The results of counting the two types of cells show that there is an increase in the number of cells which is directly proportional to time. There were different count results in each well for the two types of cells tested.

Proliferasi Pictures



Picture 1. Mikroskopis Proliferasi Sel Punca Mesenkimal (A) *Bone Marrow* dan (B) *Wharton's Jelly* with Magnification 10x after Inkubasi 24 hours



Picture 2. Mikroskopis Proliferasi Sel Punca

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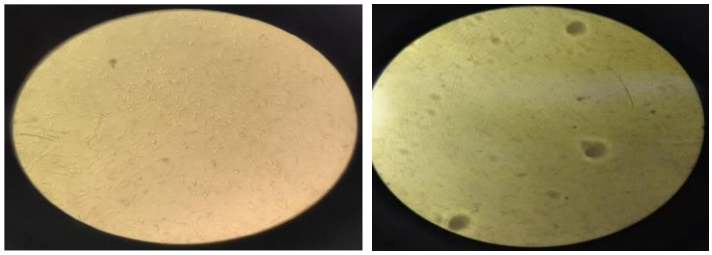
Mesenchymal (A) Bone Marrow and (B) Wharton's Jelly with 10x Magnification After 48 Hours Incubation.



Picture 3. Mikroskopis Proliferasi Sel Punca

Mesenchymal (A) Bone Marrow and (B) Wharton's Jelly with 10x Magnification After 72 Hours Incubation. Observation of cells through a microscope was documented to obtain an overview of proliferation between bone marrow and Wharton's jelly MSCs. Proliferation documentation is used to compare the proliferation results of the two cell types qualitatively. In pictures 1, 2, and 3 you can see the mesenchymal cells in the form of fibroblasts and it can be seen that in the same period of time, more cells are produced from Wharton's jelly than bone marrow. The data obtained was then analyzed, data analysis used an independent sample t-test on the Statistical Program for Social Sciences computer program with a 95% confidence interval and a significance level of 0.05.

Table 3. Statistical Test Results for Proliferation of Two Types of Stem Cells in 24 Hours

Sel	*Mean*	SD	SE	*p-value*
BM	101000	3605,5	2081,6	0,053
WJ	118333	10408,3	6009,2	

Information :
Mean *: Average*
SD *: Standard Deviation*
SE *: Standard Error*
BM *: Bone Marrow*
WJ *: Wharton's Jelly*

The homogeneity test using the Lavene test produces a value of p=0.118 so there are no differences in variance and it is considered homogeneous (p>0.05). Next, statistical analysis was carried out for stem cells within 24 hours. It was found that the p value of the T test was 0.053 (p>0.05). This value shows that there is no significant difference between the results of calculating the proliferation of bone marrow and Wharton's jelly stem cells at 24 hours.

Table 4. Statistical Test Results for Proliferation of Two Types of Stem Cells in 48 Hours

Sel	*Mean*	SD	SE	*p-value*
BM	116667	7637,6	4409,5	0,007
WJ	148333	7637,6	4409,5	

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Informatin :
Mean : Average
SD : Standard Deviation
SE : Standard Error
BM : Bone Marrow
WJ : Wharton's Jelly

The homogeneity test using the Lavene test in the 48 hour cell group obtained a value of p=1, there were no differences in variance and were considered homogeneous (p> 0.05). The result for the T test was 0.007, so there was a significant difference between the results of calculating the proliferation of bone marrow and Wharton's jelly stem cells within 48 hours.

Table 5. Statistical Test Results for Proliferation of Two Types of Stem Cells in 72 Hours

Sel	*Mean*	SD	SE	*p-value*
BM	145000	15000	8860,2	0,074
WJ	168333	7637,6	4409,5	

Informatin :
Mean : Average
SD : Standard Deviation
SE : Standard Error
BM : Bone Marrow
WJ : Wharton's Jelly

On the third day, Lavene's test obtained a value of p=0.456 so it was considered homogeneous (p>0.05). In the results using the T test, the p value was 0.074, indicating that there was no significant difference in the results of proliferation calculations between bone marrow and Wharton's jelly type stem cells within 72 hours.

Discussion

Research Results

Proliferation or the ability to multiply is one of the characteristics of stem cells. This proliferation can be carried out either asymmetrically to produce different colonies for the differentiation process or symmetrically to increase the number. This process can be influenced by many factors so that between cultures there can be differences in the speed of proliferation.

Based on the results of research conducted on two types of MSC at the Biomedical Laboratory of the Faculty of Medicine, Andalas University, qualitative results or proliferation images were obtained, there was a difference in that Wharton's jelly appeared to be more abundant than bone marrow. However, quantitatively statistically there was a significant difference at 48 hours, as well as an insignificant difference at 24 hours and 72 hours in proliferation results between bone marrow MSC and Wharton's Jelly MSC. From the cell count data, it is known that WJ MSCs are faster in proliferating compared to BM MSCs.

Insignificant differences occurred in the first 24 hours of culture but the p value given was close to significant, during this duration a lag phase occurred in cell culture where both

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types of cells experienced attachment to the substrate, cell spreading, and preparation of cells to enter the cycle, as well as initiation. to increase cell number. Within 48 hours the culture entered the log phase where the cells were experiencing rapid growth and division, the proliferation ability of both cells was visible and there was a significant difference in results between the two. At 72 hours the results were not significant, Wharton's jelly, which was faster and produced more cells, experienced a slowdown in growth due to entering the plateau phase which occurs when the cells reach confluence, namely where the cell density is high and the substrate surface for cell growth has been used, while bone marrow can still grow on the substrate.[13]

Another comparison result with two MSC cells from different sources by Hass, et al, namely between bone marrow MSC and umbilical cord MSC showed similar results. These two cells both represent adult tissue MSCs and MSCs originating from birth associated tissues, where umbilical cord MSCs have a higher proliferation capacity so they divide more quickly. The population produced by MSC from birth associated tissues is greater than that from bone marrow in the same time.[19]

In the study, the cell density used at the start was the same, namely 1x105 cells/mL. The same passivity is used between the two cells, namely P5. There is also no difference in the plastic surface quality factor because the same type of flask was used when culturing. Thus, the initial density, passage number and plastic surface quality factors do not affect the results of proliferation between the two types of cells because there are no differences.

Furthermore, there are culture medium and supplement factors that also influence MSC proliferation. The research used the same culture medium, namely alpha MEM, which was allegedly the most suitable culture medium for the isolation and expansion of MSCs.[19] The serum used was 10% Fetal Bovine Serum (FBS) in both types of cells studied. These two factors also did not influence differences in proliferation of either BM or WJ MSC in the study.

The different factor between these two types of MSC cells is the source of the cells themselves. Bone marrow MSCs are derived from the adult spinal cord and Wharton's Jelly MSCs are derived from extraembryonic tissue. In addition, the age of the donor can also play a role in influencing the proliferation results. Bone marrow MSCs derived from adults are slower to proliferate compared to the results provided by WJ MSCs. Wharton's Jelly MSC itself comes from extraembryonic tissue, including birth associated tissues, so it includes tissue that is formed with the fetus. This tissue is very young in terms of the age of adult tissue belonging to BM MSCs so that both cell source factors and donor age or tissue age have an influence on the research results.

The influence of these factors is in accordance with research conducted by Choudhery, et al which compared the proliferation of stem cells from adipose tissue (adult tissue) with stem cells from umbilical cord tissue. From this research, it was found that umbilical cord tissue proliferates more quickly.[20] As well as research by Alves, et al regarding the characteristics of MSCs which are related to the age of the donor, resulting in different molecular phenotypes, proliferation abilities and also different differentiation abilities.[21]

Apart from the factors above, there are other factors that influence MSC proliferation. Research by Stolzing, et al shows that high glucose affects stem cells. Glucose as a cell energy

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source, if given in high concentrations, damages cellular function, induces premature aging and apoptosis, and reduces the number of colony forming units (CFU) thereby reducing the rate of proliferation.[22]

There is also research on the role of antioxidants on MSCs, namely the role of ascorbic acid, where ascorbic acid can increase proliferation and maintain the differentiation ability of MSCs. In their research, Choi, et al have evaluated the effects of ascorbic acid on MSCs. It was found that different concentrations of ascorbic acid had different effects on MSC activity. Low concentrations of ascorbic acid enhance the proliferation process while high concentrations of ascorbic acid induce osteogenesis and adipogenesis in MSCs.[23]

Mesenchymal Stem Cells, which are tissue without characteristics, will be activated by signals so that the MSCs can self-renew and differentiate. For this reason, a mediator is needed to control the activity of MSC. The control carried out is in order to maintain the MSC population, prevent excessive proliferation, and induce differentiation. The mediators in question can be growth factors, hormones or cytokine.

Growth factor, which is an example of a mediator, is a factor that greatly influences stem cell activity. Administration of growth factors such as fibroblast growth factor influences proliferation and produces large numbers of MSC cells in culture.[24] Coutu, et al's research indicates that fibroblast growth factor receptor may be involved in self-renewal by inhibiting cell aging.[24] Apart from that, there is also transforming growth factor beta which is involved in many cellular processes such as cell survival, proliferation, differentiation, growth, apoptosis, homeostasis, and functions as a regulator of MSC self-renewal so that it is used for expansion and differentiation of MSCs in-vitro and in vitro. -vivo.[25]

Various studies also show a relationship between oxygen levels and the rate of proliferation of MSCs. MSC survival and proliferation are increased by maintaining cells at low oxygen levels (below 21% O2). In research using bone marrow MSCs, Lennon et al observed that BM MSCs cultured in 5% O2 produced 40% more cell proliferation than normal cultures.[26] Meanwhile, research using WJ MSC by Nekanti resulted in increased proliferation results in WJ MSC with 2% O2 culture, namely 1.87x1010 ± 8.9x109 cells compared to WJ MSC culture in normoxia, namely 1.46x109 ± 5.49x108 cells from a total of 10 passages.[27]

Research by Liu, et al on bone marrow MSCs explains that hypothermia is one of the factors that contributes to influencing MSC proliferation. Where hypothermia inhibits the proliferation and differentiation of stem cells. However, MSCs have small ubiquitin-like modifiers (SUMO) proteins that are sensitive to reactions caused by temperature stress. This protein has a protective effect on MSCs. Hypothermic conditions result in increased levels of SUMO modification of several proteins in MSCs. In the research, four SUMO target proteins were found, namely anti-proliferating cell nuclear antigen, octamer-binding transcription factor 4, p53, and hypoxia-inducible factor-1α. This SUMO modification is useful for maintaining proliferation, inhibiting differentiation, and increasing BM MSC resistance to adverse conditions. Meanwhile, knockdown of SUMO 1/2/3 induced rapid cell senescence of BM MSCs and inhibition of SUMO conjugating enzymes reduced the rate of cell proliferation and increased the proportion of BM MSCs that differentiated into nerve cells. From this

research it was found that the SUMO pathway is involved in hypothermic stress and SUMO modification is an important protective mechanism for BM MSCs in unfavorable conditions.[16]

In the proliferation picture, it was found that MSCs were thin and long fibroblast cells. The number of cells increases as time increases, and the resulting cells have the same shape. The process that occurs shows symmetric division activity which aims to form cells that are similar to parent cells.[28] There is no difference in cell morphology between BM MSC and WJ MSC microscopically, this is in accordance with research conducted by Talebian, et al where the morphology and markers of both cells are the same.[12] However, in terms of proliferation or qualitatively, there is more Wharton's jelly than bone marrow and in terms of calculating the proliferation results according to the number of cells produced, Wharton's jelly is more abundant than bone marrow.

Under culture conditions, the proliferation of MSCs is very inconsistent as a result of which the potential given is sometimes high and sometimes low and greatly affects their application in regenerative medicine. Research on the therapeutic potential of MSCs is still in its early stages and requires a lot of research before they are routinely used as cell therapy. Currently, there is still debate about how the self-renewal potential, differentiation, migration and immunomodulation mechanisms of MSCs can be controlled.[29]

CONCLUSION

There are qualitative differences in the proliferation picture between MSC bone marrow and Wharton's jelly. There were quantitative differences in proliferation results between bone marrow and Wharton's jelly MSC cell types, the difference in results was statistically significant at 48 hours, while at 24 hours and 72 hours the differences obtained were not significant. Different cell sources and the age of the tissue when isolated have an influence on proliferation results.

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