TITLE: Use of cadaveric stem cells: analysis of literature

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ABSTRACT

Determination of Post Mortem Interval (PMI) has always been based on empirical analysis of microdata not always endowed with sufficient reliability. Due to its significancy in medico-legal issues, PMI estimation needs to be assessed by applying new and more reliable methods and/or biomarkers. Considering the growing interest and use of stem cells taken from cadaveric tissues and the success in their isolation from death donors, with the maintenance of vitality and regenerative capacity, we evaluated the Literature "state of the art" on this topic to understand if those stem cells could also be used for thanatochrologic estimation.
The results obtained from Literature analysis show the possibility of using these cells as a marker for the post-mortal interval. In particular Mesenchymal Stem cells, isolated from adipose and muscular tissues, can be used to evaluate their regenerative capacity over time according to the PMI.

INTRODUCTION

Post mortem interval (PMI) is defined as the elapsed time since the death of an individual. Assessing PMI is one of the most difficult task and recurrent challenge in forensic pathology due to the influence of various intrinsic and extrinsic factors, but it is of fundamental importance in medico-legal issues.
Due to its significance and complexity, PMI estimation needs to be assessed by applying new and more reliable methods and/or biomarkers and this, in recent years, is reflected by an increasing focus of research in thanatochronology.
Several methodological approaches have been proposed but, to date, none of these resulted to be reliable for forensic purposes.
Considering the growing interest of regenerative medicine in cadaveric stem cells with a view to minimize ethical problems associated with their obtainment, we evaluated the Literature "state of the art" on this topic to understand if those stem cells could also be used for thanatochrologic estimation.

MATERIALS AND METHODS:

A review of publications was performed using PubMed database. The search was limited to work and studies published in English. Key words included were: stem cells, forensic medicine and/or cadaver.
373 articles were found. Exclusion criteria were: case reports, trials, reviews, book chapters, articles with unavailable fulltext and studies performed on brain dead but beating heart donors.
A total of 91 studies were retained, involving both human and animal cadavers.

RESULTS:

15 of the analyzed articles used only animals of different specimens, 65 focused just on human cadavers, 7 compared results between human and animals cadavers while the remaining 4 compared results between human cadavers and living donors.
The most sampled tissues were the ones derived from eye ball like corneas, conjunctiva, retina and ciliary body (30 articles), followed by bone marrow (23 articles) and central nervous system (14 articles).
Considering the type of stem cells studied, large majority of Literature focused on limbal stem cells, mesenchymal stem cells and hematopoietic stem cells with 18, 16 and 13 studies respectively.
All the articles aimed at finding useful tools for regenerative medicine purposes, while 2 studies also considered data of medico-legal interest, but only as collateral observations.

DISCUSSION:

The aim of this work is to evaluate the possibility of using stem cells as a marker for post mortem interval estimation in medico-legal issues. The idea to focus on cadaveric stem cells arised from the growing interest, especially in regenerative medicine field, on deceased donors in order to avoid ethical controversies.
Literature analysis permitted to underline that cadaveric stem cells are successfully isolated from various tissues and that, within a certain timeframe, they maintain viability and proliferative capacity. To evaluate which stem cells could be most suitable for forensic purposes, we initially focused on the most studied organs in Literature which resulted to be eye, bone marrow and the central nervous system. However, none of these organs are particularly useful in medico-legal analysis as they undergo rapid degradation after death, cannot be sampled in all the contexts (i.e. site inspection) and moreover are often affected by pre-death patients clinical conditions.
We then focused on the most studied types of stem cells that resulted in limbal, mesenchymal and hematopoietic by analysing 18, 16 and 13 articles, respectively.
Of these three types of cells, the first and third ones are collected almost exclusively from eye ball tissues and bone marrow respectively, and therefore are scarcely useful for forensic purposes for the reasons afore mentioned, while mesenchymal cells are of greater interest as they derive from various tissues, (see Table 1).
In particular muscular and adipose tissues are considered superior by some studies in terms of proliferative and differentiative capacity if compared to other tissues such as bone marrow. Moreover these tissues are very resistant to ischemic insults, are easily accessible for sampling and they are little affected by the most frequently pre-existing pathological conditions and by the cause of death of an individual.

CONCLUSIONS

Despite the growing interest and use of stem cells taken from cadaveric tissues and the success in their isolation from death donors, with the maintenance of vitality and regenerative capacity, very

little attention is given to their potential use in forensic medicine, in particular for thanatochronological purposes.
The results obtained from Literature analysis, although still limited, show the possibility of using these cells as a marker for the post-mortal interval. In particular adipose and muscular tissues can be used also in comparison, to evaluate the regenerative capacity over time of stem cells according to the PMI.

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Table 1

FIRST AUTHOR	AIM	PMI	SAMPLES	CASE NUMBER	TISSUE	MAIN ANALYSIS
Kisiel A.H.	Compare muscle and periosteum derived MSC to adipose and ne marrow derived MSC	Immediately after euthanasia	Dogs	7	Adipose tissue, muscle, periosteum, bone marrow	Differentiation analysis
Ahrens N.	Compare MSC content in different sites of extraction	Not specified	Human	Not specified	Vertebral bone marrow	Quantification of cells
Alhadlaq A.	Create a tissue-engineered human-shaped mandibular condyle	Immediately after euthanasia	Rats	Not specified	Tibial and femural bone marrow	Isolation of MSC
Radtke C. L.	Compare proliferation capacity and osteogenic potential of muscle and periosteum derived MSCs in comparsion with bone marrow and adipose tissue-derived MSCs	Immediately after euthanasia	Horses	10	Muscle tissue, periosteal tissue, bone marrow(sternebrae) and adipose tissue	Proliferation and differentiation analysis
Eslani M.	Evaluate anti-angiogenic properties of corneal derived MSCs	Not specified	Human and Mice	Not specified	Cornea	Anti-angiogenic effects of MSC secretome
Chahla J.	Identify, characterize and compare MSCs in varous menisci zones	Immediately after death and stored at 4°C	Human	7	Menisci	Isolation and proliferation capacity analysis
Kami D.	Analysis of possible cardiac MSCs use in trasplants	24h	Mice	Not specified	Heart	Proliferation and differentiation analysis
Kamishina H.	Evaluation of cell surface neuronal and glial-specific markers presence on MSCs	Immediately after euthanasia	Dogs	5	Bone marrow(iliac crest)	Identification and expression of neuronal and glial markers
Kim J.	Investigate the immunologic properties of pancreatic islet-derived MSC compared with bone marrow MSC	Immediately after death	Human	9	Pancreas	Differentiation potential, analysis of cell surface markers, metabolism, gene

						expression levels
Shikh Alsook M. K.	Find out if viable MSCs colud survive in cadaveric tissue from adult equine ligaments up to 72 hours of post-mortem and to assess their ability (I) to remain in an undifferentiated state and (II) to divide and proliferate in the absence of any specific stimulus	48-72h	Horses	4	Ligaments	Proliferation and differentiation capacity
Reisbig N. A.	Create a bioactive synovium scaffold by infusing decellularized synovial-derived extracellular matrix (synECM) with synovial-derived mesenchymal stem cells (synMSCs)	Immediately after death	Horses	3	Synovium	Isolation for cotransduction
Parks K. S.	Further evaluated th MSCs coculture system for use with isolated humans islets	Not specified	Human	Not specified	Bone marrow and umbilical cord	Isolation for co-colture
Samaeekia R.	Effect of human corneal MSC-derived exosome on corneal epithelial wound healing	Not specified	Human	Not specified	Cornea	Isolation and exosome analysis
Valente S.	Find alternative source of MSC	12h	Human	3	Vascular tissue	Proliferation and differentiation capacity
Saito T.	Confirm whether human postmortem ASCs can be collected and culutre-expanded from cadavers	21-177h	Human and mice	30 (Human)	Adipose tissue	Viability of cells
Cavallo C.	Find alternative sources of MSCs	Within 24h	Human	Not specified	Adipose tissue and bone marrow	Proliferation and differentiation capacity