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Therapeutic effects of human placenta

Unnatee Vidyadhardeore, Pranjali Rohidaspatil, Satnam Sampatrathod.
Department of pharmacy, Shastry Institute of Pharmacy Erandol, Jalgaon

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ABSTRACT - Human placental extract has been used to treat fatigue, postmenopausal symptoms, wound healing, and growth retardation in Korea. Combined with acupuncture therapy, placental extract extends its therapeutic limit to pain control. Recently, we have reported acupuncture point injection (API) with placental extract modulated inflammation-involving pain symptoms in chronic pain diseases. In order to rehabilitate patients suffering from chronic pain and restricted joint mobility, placental extract was injected into acupuncture points localized on the joints, surrounding muscles acting in concert with the joints, and paravertebral muscles affecting the innervation of the joints. Here, we describe the pathology of pain syndromes including neck pain, back pain, shoulder pain, knee arthritis, fibromyalgia, and complex regional pain syndrome and propose methodology of APIs with placental extract in treating these pain diseases.

Keywords - placental extract, acupuncture point injection, regeneration, anti-inflammation, neck and back pain, shoulder pain, knee arthritis, fibromyalgia, complex regional pain syndrome, inflammatory.

INTRODUCTION–

Placental structures, capable to persist in a genetically foreign organism, are a natural model of allogeneic engraftment carrying a number of distinctive properties. In this review, the main features of the placenta and its derivatives such as structure, cellular composition, immunological and endocrine aspects, and the ability to invasion and deportation are discussed. These features are considered from a perspective that determines the placental material as a unique source for regenerative cell therapies and a lesson for immunological tolerance. A historical overview of clinical applications of placental extracts, cells, and tissue components is described. Empirically accumulated data are summarized and compared with modern research. Furthermore, we define scopes and outlooks of application of placental cells and tissues in the rapidly progressing field of regenerative medicine.

The human placenta is a unique temporary organ which ensures mutual coexistence of the organisms of mother and fetus, determining growth and development of the latter [1]. Initially, it was believed that the fetus and placenta are closely related genetically to the mother; but with the development of assisted reproductive technology of the egg donation, it became clear that their genotypes could be completely foreign [2], which can be regarded as a natural model of engraftment after allogeneic transplantation. The main functions of the placenta are ensuring the supply, growth, and development of the fetus, as well as removing metabolic products and preventing immune rejection [1]. Since the placenta is a provisional organ, it becomes a salvage material after delivery [3]. For decades, clinicians and researchers work on the application of the placenta for therapeutic purposes, initially in the form of extracts and cell or tissue transplants, thus accumulating substantial empirical experience [4, 5]. However, at the same time, a large amount of research was little systemized and not always correlated with conventional pharmaceutical and other methods of treatment. Recent developments of cell therapy approaches along with opportunities for autobanking significantly increased the interest in the placenta as a source of biological material. Novel studies revealed a number of typical features of placental-derived cells, which define the direction of clinical use [6]. The major aim of this review was to identify and systemize general properties specific to various biological products of placental origin and characterize the most promising directions for their clinical application based on the analysis of data available in the scientific literature. Since placental structures have been used in a broad range of therapies, in our analysis, we have only considered the data, which have been confirmed repeatedly by several independent groups at various time points

Research on human placental extract began to thrive from the description on the method

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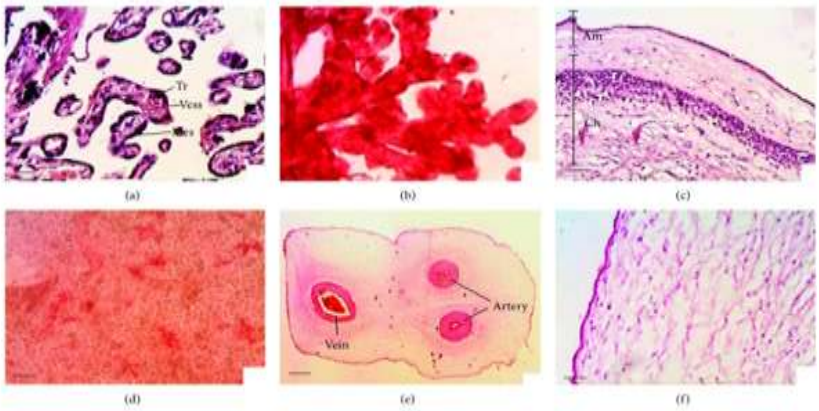
of its preparation by Russian ophthalmologist Filatov [7]. Filatov initially observed that grafting-preserved human corneas had better clinical outcomes than freshly isolated ones. He convinced that isolated tissues readjusted themselves to develop biogenic stimulators under unfavorable environmental factors. He advocated the principle of therapeutic tissues which could exhibit curative effects by adapting themselves to the tissues affected by the pathological process. Since placenta is a storehouse of potent biogenic stimulators, the application of placental extract ranges from immunology, stem cell research, genetics, and cancer research to tissue engineering. Placental extracts were demonstrated to contain wide range of peptides, proteins, minerals, amino acids, nucleotides, carbohydrates, and steroid hormones.

Experimental evidence has accumulated on the therapeutic effects of placental extracts. One of the most important roles of the placenta is to protect the embryos from oxidative stress, and therefore, placental extract has antioxidative properties [8]. Antioxidant properties of placental extract are usually associated with the protein components, especially alpha-fetoprotein [9]. Injecting placental extract to a wound margin [10] or applying placental extract topically to chronic nonhealing wounds [11] promoted healing of injured tissues. This mechanism appears to be related to an increase in transforming growth factor-beta (TGF-β) in the early phase of wound healing and vascular endothelial growth factor (VEGF) in the late phase [11]. The regeneration of sciatic axons by placental extract injection was validated by increased synthesis of regeneration-related protein factors such as GAP-43 and Cdc2 [12]. Application of placental extract in menopausal disorders allowed reducing the number of hot flushes and normalized hormone profiles [13]. Experimental animal model studies showed that placental extract decreased symptoms of fatigue and increased resistance to physical stress [14]. Placental extracts were also demonstrated to have anti-inflammatory effects in both animals and humans. In adjuvant-induced polyarthritic rats, injection of placental extract was demonstrated to alleviate arthritic symptoms including joint destruction and expression profiles of inflammatory cytokines [15]. Intra-articular injection of placental extract reduced deformity of knee joints and inhibited matrix metalloproteinase-2 and -9 activities of cartilages of osteoarthritic knee joints in rats [16].

Development of the Placenta -

During pregnancy provides the key to understand its structural and functional peculiarities. At the stage of 8 blastomeres, the blastocyst divides into embryoblast and trophoblast. Trophoblast forms villi and first primary, containing only the trophoblast, then secondary, containing the stroma (embryonic mesenchyme), and later tertiary, containing the vessels (Figures 1(a) and 1(b)). At the same time, division of the trophoblast into syncytium and cytotrophoblast takes place. Implantation processes and trophoblast invasion occur through the enzymatic destruction of the endometrium and decidua of the uterus and layering of the resulting lacunae with trophoblast cells, replacing the choroid of the spiral arteries with trophoblast, which prevents thrombosis and makes the arteries refractory to vasopressor agents. After 6–8 weeks of pregnancy, the villi remain only on the placental site. The rest of the villi become atrophied and the smooth chorion, containing significant amounts of the trophoblast elements, is being foformed17,16].



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Morphology of placental components: (a, b) placental tissue (villi): Tr: trophoblast; Vess: vessels; Mes: mesenchyme; (c) fetal membranes: Am: amniotic membrane; Ch: chorionic membrane; (d) surface cells of amniotic epithelium; (e) cross-section of the umbilical cord; (f) umbilical cord tissue. Staining: (a, c, e, and f) hematoxylin-eosin, sections; (b, d) neutral red, native preparation. Scale bars: (a, b, c, d, and f) 50 μm; (e) 1000 μm.

Preparation of placental extract -

Treatment of pain based on anti-inflammation and regeneration –

Musculoskeletal disorders are the most frequent cause of disability in the modern world, and the prevalence of these diseases is rising at an alarming rate. The most prominent reason for loss of joint mobility and function is chronic pain, which leads to impaired quality of life. Current therapies to alleviate pain have limited effectiveness, and some drugs produce unwanted negative side effects, thereby precluding their long-term use.

Nociceptive receptors are located throughout the joint. It has been identified in the capsule, ligaments, menisci, periosteum, and subchondral bone. If a noxious mechanical factor or inflammatory mediator is applied to the joint, the firing rate of the afferent nerve increases dramatically, and the central nervous system interprets this nociceptive activity as pain [19]. Transient pain is induced and serves as a physiological warning at brief, high-intensity stimuli, which produce little or no tissue damage. However, in chronic pain conditions, there may be spontaneous pain, as well as intermittent pain, which is induced by persistent inflammation from structural damage or functional degeneration. Chronic pain is also associated with complex changes in peripheral and central signal processing [20].

It is accepted that inflammation and the inflammatory response play pivotal roles in the occurrence, as well as progress of pain. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors, and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and inflammatory response. Activation of pain receptors, transmission of pain signals, and modulation of neuroplasticity all belong to a continual spectrum of inflammation and inflammatory response.

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from one person to another and may have variations in the same person at different times. Various symptoms of pain syndromes are attributed from corresponding inflammatory profiles of discrete pain syndromes. The key to treat pain syndromes is inhibiting the production of inflammatory mediators at the same time regenerating injured or degenerative tissues. The term “regeneration” is used to describe the phenomena that allow an organism to reconstitute the structure damaged by injury and recover the functional homeostasis. A successful outcome is one that results in less inflammation, more regeneration, and thus less pain.

Anti-inflammatory effects of acupuncture point injection with placental extract -

Acupuncture has been used in the treatment of several diseases for at least 5000 years in Asia. In the western society, acupuncture has become a central part of complementary medicine. An increasing number of patients, especially those suffering from chronic diseases, are seeking acupuncture treatment. The widespread application of acupuncture includes the treatment of infections, inflammatory diseases, autonomic dysfunction, psychological disorders, musculoskeletal diseases, and many other illnesses [21].

The neural activation by acupuncture was investigated by many researchers. With the stimulation of vision-related acupuncture points, visual cortices of the brain were found to be stimulated [22]. Liu et al. [23] and Li et al. [24] reported that the C-fiber rich afferents of the deep tibial nerve coincided with acupuncture points, implying rich distribution of nerve fibers/reflex complexes at acupuncture points. Abraham et al. [25] also proved that the acupuncture points contained a significantly higher number of transient receptor potential vallinoid type 1-positive Aδ- and C-fibers as compared with nonacupuncture points. Gao et al. [26] demonstrated that the enhancement of gastric motility induced by acupuncture point ST36 stimulation was mediated by N-methyl-D-aspartate receptors.

In acupuncture, the insertion of needle induces marked changes close to the needle in all different tissues that are penetrated. These peripheral events might improve tissue function

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through dilation in the skin due to axon reflexes [27]. Additional activation can be obtained through manipulation of the needle or electro-stimulation at different frequencies. Studies have shown that manual acupuncture (back-and-forth motion or up-and-down motion) or electrical stimulation in specific frequencies applied to acupuncture points can facilitate the release of specific neuropeptides in the central nervous system [28]. This activation is demonstrated to elicit profound physiological effects and even activate self-healing mechanisms [29]. Although the effect of manual acupuncture or electro-acupuncture is comparative to the effects of nonsteroidal anti-inflammatory drugs and opioid analgesics [30], maintenance of needles might be cumbersome, particularly in agitated animals. In order to overcome this disadvantage, other techniques might be used for stimulation of acupuncture points.

Acupuncture point injection (API) is a new acupuncture technique which combines acupuncture and medication. API is widely used to enhance and prolong the effect of stimulation of acupuncture points [31]. API with placental extract can be used to control pain syndromes due to anti-inflammatory effects from each member. Numerous uncontrolled trials, as well as a limited number of controlled trials, have been published after short-term or long-term use of acupuncture in the treatment of inflammatory diseases. The direct and indirect effects of acupuncture on regulation of inflammatory mediators such as neuropeptides, cytokines, and vasoactive substances have been assessed [32]. Even though there are some pitfalls such as relatively small number of patients and incompletely described methodological procedures, the results clearly show a beneficial effect of acupuncture in the reduction of symptomatic inflammatory response. As well, anti-inflammatory effects of placental extracts were fully evaluated. Porcine placental extract was shown to protect the contact hypersensitivity of skin by modulation of immunoglobulin E production [33]. Animal model studies showed that placental extracts reduced the concentration of free radicals, inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor (TNF), and interleukin-1 (IL-1) at the same time increasing the colony formation of progenitor cells in vitro [34]. Clinical trials of API with placental extracts showed anti-inflammatory effects in pain diseases. Injection of placental extract to acupuncture points ameliorated various inflammation-associated symptoms of complex regional pain syndrome [35, 36].

Effect of human placental extract on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women -

In Korea, human placental extract (HPE) has recently been used to treat various diseases (chronic liver diseases, menopause syndrome, chronic fatigue, skin pigment diseases, etc.), but evidence-based studies are not yet sufficient. The aim of this study was to examine the effects of HPE on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women in a randomized controlled trial[37].
Korean women, aged 40 to 64 years, with menopausal symptoms and fatigue were recruited as participants. The women were randomly assigned to a placebo group or an HPE group. The HPE group received subcutaneous injections of HPE in the abdomen for 8 weeks, whereas the placebo group received normal saline. Then, the Menopause Rating Scale, and Fatigue Severity Scale, and Visual Analog Scale were administered, and risk factors for cardiovascular disease were assessed [37].

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