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SCIENTIFIC ARTICLE

Total knee replacement induces peripheral blood lymphocytes apoptosis and it is not prevented by regional anesthesia – a randomized study

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KEYWORDS
Total knee replacement;
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Abstract
Background: Among the many changes caused by a surgical insult one of the least studied is postoperative immunosuppression. This phenomenon is an important cause of infectious complications of surgery such as surgical site infection or hospital acquired pneumonia. One of the mechanisms leading to postoperative immunosuppression is the apoptosis of immunological cells. Anesthesia during surgery is intended to minimize harmful changes and maintain perioperative homeostasis. The aim of the study was evaluation of the effect of the anesthetic technique used for total knee replacement on postoperative peripheral blood lymphocyte apoptosis.
Methods: 34 patients undergoing primary total knee replacement were randomly assigned to two regional anesthetic protocols: spinal anesthesia and combined spinal–epidural anesthesia. 11 patients undergoing total knee replacement under general anesthesia served as control group. Before surgery, immediately after surgery, during first postoperative day and seven days after the surgery venous blood samples were taken and the immunological status of the patient was assessed with the use of flow cytometry, along with lymphocyte apoptosis using fluorescent microscopy.
Results: Peripheral blood lymphocyte apoptosis was seen immediately in the postoperative period and was accompanied by a decrease of the number of T cells and B cells. There were no significant differences in the number of apoptotic lymphocytes according to the anesthetic protocol. Changes in the number of T CD3/8 cells and the number of apoptotic lymphocytes were seen on the seventh day after surgery.
Conclusion: Peripheral blood lymphocyte apoptosis is an early event in the postoperative period that lasts up to seven days and is not affected by the choice of the anesthetic technique.

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PALAVRAS-CHAVE
Artroplastia total do joelho;
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Linfócitos;
Apoptose

Artroplastia total do joelho induz apoptose em linfócitos de sangue periférico e não é evitada por anestesia regional – estudo randômico

Resumo
Justificativa e objetivo: Dentre as muitas alterações causadas por uma ferida cirúrgica, uma das menos estudadas é a imunossupressão pós-operatória. Esse fenômeno é uma causa importante das complicações infecciosas relacionadas á cirurgia, como infecção do sítio cirúrgico ou pneumonia nosocomial. Um dos mecanismos que levam à imunossupressão pós-operatória é a apoptose de células imunológicas. Durante a cirurgia, a anestesia se destina a minimizar as alterações prejudiciais e manter a homeostase perioperatória. O objetivo deste estudo foi avaliar o efeito da técnica anestésica usada para artroplastia total de joelho sobre a apoptose em linfócitos de sangue periférico no pós-operatório.
Métodos: 34 pacientes submetidos à artroplastia total primária de joelho foram randomicamente designados para dois protocolos de anestesia regional: raquianestesia e bloqueio combinado raqui-peridural. Onze pacientes submetidos à artroplastia total do joelho sob anestesia geral formaram o grupo controle. Antes da cirurgia, logo após a cirurgia, durante o primeiro dia de pós-operatório e sete dias após a cirurgia, amostras de sangue venoso foram colhidas e o estado imunológico do paciente foi avaliado com o uso de citometria de fluxo, juntamente com apoptose de linfócitos usando microscopia de fluorescência.
Resultados: Apoptose em linfócitos de sangue periférico foi observada imediatamente no pós-operatório e acompanhada por uma redução do número de células T e B. Não houve diferença significativa no número de linfócitos apoptóticos de acordo com o protocolo anestésico. Alterações no número de células T CD3/8 e no número de linfócitos apoptóticos foram observadas no sétimo dia após a cirurgia.
Conclusão: Apoptose em linfócitos de sangue periférico é um evento precoce no período pós-operatório que dura até sete dias e não é afetado pela escolha da técnica anestésica.

Introduction

Surgical trauma leads to a complex systemic response including sympathetic nervous system activation, endocrine response, and inflammatory and immunological disturbances. Simultaneously with inflammatory response activation, which reduces the surgical stress damage area and facilitates repair processes, immunological system impairment occurs. This mechanism seems to have a defensive function – the organism defends itself from the autoimmunological response in a situation of its own antigens' excess and a stimulation of the processes of their recognition. Unfortunately, it also leads to adverse consequences – direct damage of natural defensive barriers such as skin and mucous membranes in association with impairment of defensive mechanisms that increases the possibility of infections. In oncologic surgery that also means metastatic progression and acceleration of neoplasmal disease.

Postoperative lymphopoenia is a phenomenon that has been known for a long time, and it applies to all lymphocyte populations and its intensification is directly proportional to the extent of the injury.[1] It is caused by a series of perioperative events and one of them has been intensively examined in recent years. Apoptosis is the process of programmed cell death, a term which was proposed in 1972 by Kerr et al. to describe morphologically different types of cell death.[2] Intensive research which has been continued in the years following allowed the specification of mechanisms leading to programmed cell death and precise control of the cell count. It is especially important in relation to the immunological system, since cell deficiency involves uncontrolled tumor cell growth and increases the risk of infection, whereas excess of immunological cells may lead to autoimmunological response. The main apoptosis pathways are: extrinsic, associated with particular ''death ligand'' (FasL, CD195), and intrinsic – mitochondrial, which depends on physical and chemical factors such as hypoxia or toxins that lead to changes in mitochondrial structure. The third path described in relation to cytotoxic lymphocyte T is perforin/granzyme-mediated apoptosis.[3]

Surgical trauma includes direct tissue damage as well as other factors including: administered anesthetics, blood loss followed by blood transfusions, hypothermia, immobility, in some procedures also general or local ischemia and reperfusion injury. All of the above can induce apoptosis of immune cells. Clinical research showed an influence of surgical procedures on circulating blood lymphocyte apoptosis.[4] This raises a question about an optimal anesthetic technique and anesthetics used in it. Research focused on the influence of anesthetics on lymphocyte apoptosis in *in vitro* conditions shows pro-apoptotic effect of almost all inhalational, intravenous and local anesthetics.[5,6] Unfortunately, data collected from clinical research are ambiguous. Comparative research from 2009 did not indicate regional anesthesia being superior to general anesthesia (GA).[7]

Over the last few years several interesting retrospective studies focused on estimating the long-term effects of regional anesthesia were presented. They proved that