Does cisatracurium at a clinical dose attenuate the immunosuppression after surgery in smoking patients with non-small cell lung cancer?

Wen-qin Sun*, Dao-Bo Pan*, Ai-Guo Zhou* and Hong Mo*

Immunosuppression is a feature of the postoperative stress response and is associated with anesthesia, blood transfusion, hypothermia, mechanical ventilation, and the patient’s underlying disease. There is a shift from a T helper cell 1 (Th1) to a Th2 immune response in those patients with non-small cell lung cancer after surgery, which appears to be associated with infections, sepsis, and cancer formation and progression.

Cisatracurium is a benzyl isoquinoline non-depolarizing muscle relaxant, which is widely used during anesthesia due to its Hofmann degradation independent of liver and kidney functions, no release of histamine and its intermediate duration. It is well known that nicotine can inhibit immune function and attenuate systemic inflammatory responses via activating α7 nicotinic acetylcholine receptors (nAChRs), which is termed the cholinergic anti-inflammatory pathway. Besides blocking muscle nAChRs, non-depolarizing muscle relaxants, such as d-tubocurarine, can also block α7 nAChRs expressed on multiple-type cells in vitro, but limited data is available in clinical settings.

The hypothesis

Cisatracurium at clinical dose may be useful in attenuating postoperative immunosuppression in smoking patients with non-small cell lung cancer.

Evaluation of the Hypothesis

Nicotinic acetylcholine receptors (nAChRs) are composed of five receptor subunits, including α1 to α10, β1 to β4, γ, δ, and ε, which form ligand-gated ion channels. According to their physiological distribution, nAChRs are classified as either muscle or neuronal nAChRs. In neurons, α7 nAChR assembles as a homopentamer composed of five individual α7 subunits that form a central pore with ligand binding at subunit junctions. α7 nAChR also widely expressed in human immune cells, including T lymphocytes, B lymphocytes, dendritic cells, monocytes, macrophages, neutrophils, and microglia cells. These receptors play an important role in controlling angiogenesis, apoptosis of T cells, and the development and antibody secretion of B cells as well as down-regulating proinflammatory cytokine synthesis in macrophages and glial cells.

* MD, Department of Anesthesiology, The First People’s Hospital of Changde, Changde, China.

Corresponding author: Dr. Sun, Department of Anesthesiology, The First Affiliated Hospital of Changde, 388# People’s East Road, Changde 415003, China. Tel & Fax: +86 7367788088. E-mail: 15873666967@163.com
Nicotine, the main addictive component of tobacco, binds to various subtypes of nicotinic acetylcholine receptors that are expressed on neurons and some non-neuronal cells, such as α7 nAChRs in immune cells. Activation of α7 nAChRs by nicotine leads to elevated intracellular calcium levels sufficient to active signal transduction pathways that suppress innate and adaptive immune responses\textsuperscript{15}. Nicotine reduces T cell proliferation and the production of Th1 and Th17 cytokines\textsuperscript{16} and enhances immunosuppressive function of CD4\textsuperscript{+}CD25\textsuperscript{+} Tregs via α7 nAChR\textsuperscript{17}. There are also reports on the inhibition of antigen presentation of dendritic cells and disruption of their ability to induce Th1 lineage differentiation by nicotine\textsuperscript{18-19}. It has been reported that chronic exposure to nicotine up-regulates expression of α7 nAChRs on circulating monocytes in humans and CD4\textsuperscript{+} T cells in mice\textsuperscript{16,20}. Therefore, smoking deteriorates the immune system function in patients with lung cancer. The effects of cisatracurium on the immune response in patients with lung cancer after surgery has not been well established. Cisatracurium is able to block α7 nAChRs on immune cells because it has a similar chemical structure and more potent effect compared with d-tubocurarine which is conformed to block α7 nAChRs\textsuperscript{6}. We hypothesize that nicotine induced immunosuppression may be attenuated due to antagonizing α7 nAChRs on human peripheral blood mononuclear cells by cisatracurium, thus protecting against the postoperative immunosuppression in smoking patients with lung cancer.

**Consequences of the Hypothesis and Discussion**

If α7 nAChRs on peripheral immune cells are blocked by cisatracurium at clinical dose, it would very likely affect systemic immunity, such as enhancing Th1-type cytokines production, inducing Th1-type lymphocyte differentiation and proliferation, weakening CD4\textsuperscript{+}CD25\textsuperscript{+} regulatory T cells suppressive activity. Therefore, the administration of cisatracurium or other non-depolarizing muscle relaxants to smoking patients with non-small cell lung cancer during surgery should be given great importance and a continuous infusion with a deeper level of neuromuscular blockade is recommended.

In conclusion, the postoperative immunosuppression in smoking patients with non-small cell lung cancer may be attenuated by continuous infusion of cisatracurium during surgery. Non-depolarizing muscle relaxants may play an important role in regulating postoperative immune response in smoking patients with non-small cell lung cancer and may lower the risk for tumor development and enhance the clinical outcome of surgical treatment.
References
