

Immunological Response of Postcholecystectomy: Single Incision Laparoscopic Surgery (SILS) vs Natural Orifice Transluminal Endoscopic Surgery (NOTES)

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ABSTRACT

Introduction: Surgery evokes complex metabolic, neuroendocrine and immunological responses. These are reparatory but when exaggerated may cause immunosuppression with morbidity and mortality. It is well-known that these responses are attenuated in laparoscopic cholecystectomy, which is the gold standard for treatment of cholelithiasis. Current novel minimal access techniques of natural orifice transluminal endoscopic surgery (NOTES) and single incision laparoscopic surgery (SILS) consolidate on the gains of better cosmesis, reduced postoperative pain and rapid recovery; however, they are yet to be fully evaluated in terms of comparative advantage on immunological basis.

Aims: This study aims to compare the immunological changes following the techniques of NOTES and SILS in cholecystectomy with a view to ascribe relative advantage.

Methods: Literature review of immunological changes following NOTES and SILS from Medline, Cochrane Database, Google and SpringerLink. Cross references from list of major articles on subject were read with other relevant journals from a laparoscopic research institute library.

Results: Pneumoperitoneum affects the local peritoneal immune environment resulting in alterations in cytokine production and phagocytic function. Interleukin-1 (IL-1), tumor necrosis factor and particularly IL-6 are potent systemic mediators of the immune and acute phase response following surgery. Various animal model studies have shown that NOTES and SILS evoke similar levels of inflammatory cytokine profiles but for a late-phase tissue necrosis factor-alpha (TNF-alpha) depression with NOTES.

Conclusion: Minimal access techniques of cholecystectomy have reduced immune response compared to open surgery. There is limited immunological data available comparing NOTES and SILS postcholecystectomy. Large randomized studies are needed to ascribe immunological advantage between these two techniques of cholecystectomy.

Keywords: Single incision laparoscopic cholecystectomy, NOTES, Immune response.

INTRODUCTION

Surgery evokes complex metabolic, neuroendocrine and immunological responses. These are reparatory but when exaggerated may cause immunosuppression with morbidity and mortality. It is well-known that these responses are attenuated in laparoscopic surgery. Cholelithiasis is a major cause of morbidity in the Western world with 500,000 and 21,000 cholecystectomies performed annually in the USA and Netherland respectively.^{1,2} Open cholecystectomy was popularized by Carl Langenbuch in the nineteenth century.³ This practice has undergone a paradigm shift in the last two decades heralded by the efforts of Eric Muhe and Phillippe Mouret in 1985 and 1987 respectively, by performing laparoscopic cholecystectomy.^{4,5} Laparoscopic cholecystectomy is widely accepted and presently the gold standard for the treatment of cholelithiasis. Conventionally, this procedure is carried out through four ports but more recently through a single incision (SILS). Rapid advances in technology have led to a novel

technique of gallbladder removal through a transluminal endoscopic device. The first description of natural orifice transluminal endoscopic surgery (NOTES) is credited to Kallo et al.⁶ This has evoked much enthusiasm with the prospect of consolidating on the gains of cosmesis, reduced postoperative pain and rapid recovery. The need to compare the various aspects of both techniques thus exists.

AIMS

This study is designed to compare the immunological responses following the techniques of NOTES and SILS in cholecystectomy with a view to ascribe relative advantage.

MATERIALS AND METHODS

Literature search was conducted using Medline, Cochrane database, Google and SpringerLink. Search words were "NOTES surgery", "single incision laparoscopic cholecystectomy" and "immune response". A selection criterion for further reading was literature written in English language. Cross references,

from list of major articles on this subject and relevant journals from Laparoscopic Research Institute, India, were read.

RESULTS

Pneumoperitoneum affects the local peritoneal immune environment resulting in alterations in cytokine production and phagocytic function. Interleukin-1 (IL-1), tumor necrosis factor (TNF) and particularly interleukin-6 (IL-6) are potent systemic mediators of acute phase response following surgery, thus, are useful parameters for studying immune response following these advanced methods of cholecystectomy. Various animal model studies have shown that NOTES and laparoscopy evoke similar levels of inflammatory cytokine profiles.⁷⁻⁹ There is insufficient immunological data comparing SILS and NOTES post-cholecystectomy in human studies.

OVERVIEW OF IMMUNE RESPONSE

Immunity is the body's defense system against foreign bodies and is either innate or acquired (adapted). The acquired mechanism is highly specific for a stimulus, improving on successive exposure; however, the innate mechanism is non-specific for the antigen with no protective memory. Immune responses are generated by cellular or noncellular (humoral) mechanisms. Studies of immune response previously conducted involved peripheral blood, cytokines, C-reactive protein, histamine response and other useful parameters, including leukocyte and function, macrophage activation and delayed-type hypersensitivity.¹⁰

Systemic Immune Response

Immune response following surgery is a complex process that follows a specific pattern and has been defined based on clinical and laboratory observations. A proinflammatory immune response mediated primarily by the cells of the innate immune system is followed by a compensatory anti-inflammatory or immunosuppressive phenotype that is mediated primarily by cells of the adaptive immune system with host predisposition to septic complications.¹¹ Immune dysfunction induced by surgical trauma may comprise either an inappropriately exaggerated inflammatory response or a profound suppression of cell-mediated immunity. However, careful surgical technique by the use of a minimally invasive approach, adequate fluid replacement, and antibiotic therapy attenuate these responses. Notable mediators of immune response studies are cytokines. These are glycosylated and nonglycosylated polypeptides that act as soluble immune messengers. They are of two types—proinflammatory and anti-inflammatory. Proinflammatory cytokines include tumor necrosis factor- α (TNF- α), interleukin-1- β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8) and interferon- γ (IFN- γ). The anti-inflammatory cytokines are interleukin-10 (IL-10), IL-1 receptor antagonist (IL-1 RA), and soluble TNF binding proteins 1 and 2 (TNF-BP1 and TNF-

BP 2). The major mediators of the acute-phase response are known to be interleukin-1 (IL-1), tumor necrosis factor (TNF) and interleukin-6 (IL-6).¹² The tumor necrosis factor (TNF) and IL-1 are responsible for nonhepatic acute-phase response, including fever and tachycardia, while interleukin-6 primarily regulates the hepatic component resulting in the production of acute-phase proteins. It is suggested IL-6 also influences polymorphonuclear leukocyte-mediated inflammation via its role in stimulating the proliferation of polymorphonuclear leukocyte progenitors in the bone marrow.¹³ High levels of IL-6 have been associated with an increased severity of tissue trauma. Studies demonstrate that it affects the production of prostaglandin E, a strong immunosuppressant which induces the chemotaxis response of the lymphocytes and macrophages at the damage site.^{14,15} The other acute-phase proteins include C-reactive protein, complement factor 3, haptoglobin and serum amyloid A.

Postconventional cholecystectomy, a transient rise in pro-inflammatory cytokines, has been noted unlike in laparoscopic surgery which is characterized by a decreased acute-phase pro-inflammatory response of TNF- α , IL-1, C-reactive protein levels and IL-6.^{16,17} A case study showed a late-phase tissue necrosis factor- α (TNF- α) depression with NOTES.¹⁰ Extensive studies, both in animals and humans, have demonstrated better preservation of the immune system in minimal access laparoscopic procedures with attenuation of the fall in lymphocyte count, abrogating the decrease of monocytic HLA-DR antigen expression associated with major surgical trauma.¹⁹ Minimally invasive approaches restore the decreased IL-2, IFN- γ , and TNF- α production by T-cells observed with open surgery.²⁰

LOCAL PERITONEAL CHANGES FROM PNEUMOPERITONEUM

The prerequisite establishment and maintenance of pneumoperitoneum for minimal access cholecystectomy alters the interior milieu. Local peritoneal changes are dependent on the gas used, its pressure, duration of insufflation and temperature. These changes may be beneficial and adverse in effect. Carbon dioxide with the advantage of rapid absorption is the most common agent used for establishing and maintaining pneumoperitoneum in minimal access cholecystectomy. In an aqueous medium, carbonic acid is formed and a drop in pH after the induction of CO₂, pneumoperitoneum affects the biochemical and cellular immune function inherent to the peritoneal cavity.²¹ Morphological changes to the peritoneal endothelium may result in denudation, migration of PMN leukocytes, mast cells and macrophages. The degranulation of mast cells effect an increase in vascular permeability with supply of complement factors and opsins. Activated leukocytes and macrophages release notably, TNF- α , IL-1 and IL-6. Carbon dioxide has been shown to decrease peritoneal macrophage

release of basal TNF- α . This significant reversible inhibition of TNF and IL-1 demonstrated in macrophages incubated in carbon dioxide are not seen with helium or air.²²

Most studies on NOTES have been performed with room air to establish pneumoperitoneum. Insufflation of air through the flexible endoscopes used in performing NOTES currently is not pressure controlled. The flow rate used in the typical laparoscopy insufflators is higher. To date there is no randomized study that fully investigates the extent of immune responses following this advanced endoscopic procedures to know if physiology of pneumoperitoneum will behave in a similar way to the much studied carbon dioxide induced pneumoperitoneum of laparoscopy.

DISCUSSION

The evolutionary arc from open to laparoscopic and now no-scar cholecystectomy has facilitated improvement in patient recovery, cosmetic results and reduced pain medication. The wide acceptance of these novel therapies has fueled huge investment of time, effort and funds by researchers to indeed achieve a no-scar surgery. At present, it is advised that NOTES should be performed by a complementary team of a skilled therapeutic endoscopist and a laparoscopic surgeon, in view of the complex tasks required for its performance. Approach to the peritoneum in this experimental extension of conventional flexible endoscopy is via the stomach, colon, bladder and vagina. Laparoscopic instruments are often inserted through one or two abdominal ports to assist in the procedure (hybrid NOTES). In its pure form the transvaginal approach is used, thus making the procedure applicable to only women evoking among other issues ethical considerations. Patient acceptance between SILS and NOTES is in favor of the former.

Infection rate is an important issue for consideration. Contamination of the peritoneal cavity by enteric contents may render NOTES more immunologically invasive than previously thought with possible increased risk of infection. Few cases of intraperitoneal abscesses have been observed in some laboratory works though surgical measures of sterilization of gut prior to puncture and use of sterile overtubes are protective.²³ Bacteriostatic sterilization of equipment is generally sufficient for laparoscopy, however, bactericidal sterilization with ethylene oxide is advocated for transluminal surgery in some centres. Leakage from gastric (intestinal) closure is likely to increase the risk of infection in NOTES.

Pain is an important stimulus for immune response following surgery. Single incision laparoscopic cholecystectomy involves the use of a single skin incision which is supplied by somatic innervations. The character of this pain is sharp, stabbing and well-localized. Transluminal abdominal procedures require access to the peritoneum through viscus. Visceral pain is dull nagging and poorly localized. Viscera are sparsely innervated compared to dense and somatotopically oriented innervations

of the skin. Fewer than 7% of afferent nerves entering the spinal cord project to the viscera, and only a small fraction of these transmit sensory input to the central nervous system.²⁴ These innervations, however, sparse spread to several segments of the cord precluding the prospect of spinal/epidural anesthesia. Studies are needed to evaluate the impact of somatic and visceral pain in the context of the overall immunological profile of these novel procedures in cholecystectomy. In contrast to conventional laparoscopy there is a reduction of shoulder tip pain from irritation of the diaphragm caused by trapped carbon dioxide following single incision laparoscopy.²⁵ The paucity of large population study for transluminal surgery commonly performed using room air for pneumoperitoneum is a limitation to understanding differences in pain induced immune responses.

Anesthetic considerations play a role in the multifactorial adverse immune response following surgery. Nonspecific defenses both cellular and humoral responses with anesthetic agents produce a combination of direct and indirect effects. These have significant impact on the function and regulation of immune response. Longer operating time means longer exposure to anesthetic agents and pneumoperitoneum with strong potentials for immune status alteration. Technical difficulties and a shortage of proper equipment lead to longer operating time in NOTES. Better equipment and adequate training and experience are likely to shorten operating time.

CONCLUSION

Minimal access techniques of single incision laparoscopy (SILS) and natural orifice transluminal endoscopic surgery (NOTES) are novel techniques in the surgical removal of the gallbladder. Compared to open surgery they have a more favorable immune response. There is limited immunological data available comparing NOTES and SILS postcholecystectomy. Further large randomized studies are needed to ascribe immunological advantage between these novel techniques.

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