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EDITORIAL

Intraperitoneal wound in abdominal surgery

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Abstract

The intraperitoneal wound is often forgotten after transperitoneal surgery. This review is a on the peritoneum and the implications of peritoneal injury after surgery. This review will focus on the intraperitoneal wound response after surgical injury.

Key words: Peritoneum; Vagus nerve; Abdominal surgery; Cytokine; Laparoscopy; Inflammation

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INTRODUCTION

An abdominal operation combines a somatic abdominal wall wound with a second wound to the peritoneal cavity and viscera. Little attention has been paid the peritoneal wound that communicates directly to the brain by the vagus nerve. Traditionally most interventions have focused on producing relief from the physiological burden created by the somatic abdominal wall wound. However recent research indicates that the "forgotten" intraperitoneal wound may be clinically important especially in those who undergo extensive transperitoneal injury.

PERITONEUM

The peritoneum is a serous membrane that lines the abdominal cavity and the intra-abdominal viscera. This dynamic cellular membrane has important functions[1]. It provides a frictionless environment for movement of abdominal organs and is a metabolically active sheet of tissue that envelops the majority of the abdominal viscera and is protected by macrophage scavengers. These scavengers play a key role in the local immune response by producing local mediators such as interleukin-6 (IL-6), tumor necrosis factor (TNF-α) and oxygen radicals[2]. Furthermore the peritoneum is unique compared to surrounding organs in that it carries a lower level of anti-inflammatory pathways resulting to a greater adhesion forming pathways after injury compared to the regeneration that occurs in other organs[3]. The peritoneum is highly metabolically involved and active, enveloping the majority of the abdominal viscera[4].

Because the entire peritoneal cavity is linked *via* transcoelomic spread of immuno-humoral factors in the peritoneal fluid, it exhibits a coordinated response to injury which is generalised and not limited to the localised area of insult[5,6]. This is supported by the fact that there are much higher cytokine concentrations in peritoneal fluid than in plasma after gastrointestinal surgery suggesting that cytokine production occurs in a compartmentalised fashion within the abdominal cavity[7,8].

The nerve supply to the peritoneum is conveyed along the autonomic nervous system from the parasympathetic and sympathetic system. It can convey sensory fibres via the cranial nervous system, namely the sub-diaphragmatic vagus afferents. The sub-diaphragmatic vagal afferents, about 50000 in number are almost all made from low threshold unmyelinated (C) fibres. They convey background sensations such as mechanical stretch, satiety, fullness, nausea and vomiting sensations[9]. Afferent vagal inputs originating from the peritoneum and abdominal viscera have great potential to modulate and regulate

behaviour in humans[10,11]. Furthermore, 90% of the subdiaphragmatic vagus is entirely afferent in nature, indicating a critically important role in direct peritoneal to central nervous system signal transmission and modulation of inflammatory processes arising from the peritoneum[10,12,13].

Spinal afferent also supply the parietal peritoneal linning and mesentery of the gastrointestinal tract, and have cell bodies located in the dorsal root ganglion projecting to the dorsal horn of the spinal cord. They follow the paths of the sympathetic (splanchnic) and parasympathetic (pelvic) efferents to the gut wall[14]. All of the visceral afferents combined make no more than 7%-10% of all afferent inflow to the spinal cord[12,14].

SURGICAL TRAUMA TO THE PERITONEUM

Comparative studies of cellular immunity after laparoscopic and conventional trans-peritoneal surgery have demonstrated immunologic advantages conferred by reducing the somatic abdominal wall wound by performing minimal access laparoscopy[15]. In these animal models there appears to be a biological peritoneal advantage after laparoscopy when compared to open surgery. Authors have hence argued, that the peritoneal immune response after laparoscopic surgery is better preserved[15]. This mechanism is uncertain but has been thought to arise from smaller peritoneal incisions minimizing peritoneal stress, reduced exposure of peritoneum to solubilized pathogens in air, and minimal manipulation and handling of the organs.

A large component of the intra-abdominal afferent system (40%-45% in the colon and bladder) are by fibres normally unresponsive to stimuli that become activated only in the presence of inflammation and injury[16]. These "silent nociceptors" are different in that they are mainly concerned with tissue injury rather than mechanical stimuli such as stretch. One theory is that these class of nociceptors lead to abnormal autonomic regulations by insult which produces dramatic changes in the environment that surrounds the nerve endings with potential to excite distant nociceptors not affected by the initial insult[17]. What is also concerning about intraperitoneal nociceptors is that as they are not normally active, discharge after inflammation and injury may be greater in magnitude and duration than the discharges produced by acute injurious stimuli, which potentially makes the central effects even greater than the initial insult[18]. Transcoelomic spread of pro-inflammatory cytokines may activate areas of the peritoneum distant from the site on intraperitoneal injury. Thus downstream effects may persist for a long duration even after the initial injury is near or complete resolution.

The abdominal wall wound can be reduced significantly in size, by minimally access techniques, such as laparoscopy. When one considers procedures where the incision is the cause of the predominant metabolic insult to the patient, the benefits would appear to be obvious and of a significant clinical magnitude. For example in cholecystectomy the metabolic response is thought to be from the abdominal wall wound itself[19]. Therefore it can be postulated that this should translate into a lesser magnified sickness response and hence quicker recovery. The benefits of laparoscopic cholecystectomy are evident when compared to classic open colectomy[20] but not as obvious when compared to the small or "mini" laparotomy version of the same operation[21]. Therefore there may be a threshold size effect where further benefits are not seen.

However what is interesting is that in humans the peritoneal cytokine response is similar in laparoscopic and open colonic surgery[22,23]. Also the systemic pro-inflammatory concentrations after both surgical approaches represent only a small fraction of what is generated from the peritoneum. This suggests that the two intra-abdominal approaches are locally equally traumatic to the peritoneal cavity[22,24]. Thus it seems plausible that laparoscopic surgery does not confer an additional clinical advantage if we concentrate on peritoneal wound disruption. The intraperitoneal disruption is still the same no matter how access to the cavity is gained. A recent review on this topic in an optimized recovery setting has clinically confirmed that similar clinical outcomes can be reached between modalities[25]. Hence what seems to be rather important in abdominal surgery is whether the peritoneum as an entity is entered, dissected, and manipulated. This is demonstrated in clinical studies of aorta aneurysm repair, with trans-peritoneal aneurysmal repair resulting in significantly higher inflammatory response corresponding to slower clinical recovery compared to the extra-peritoneal approach where this is possible[26].

Operating on many organs such as colonic resection necessitates intraperitoneal injury and hence extra-peritoneal approach is not an option. In Part Ⅱ of this series we will focus on possible new methods to manipulate the intraperitoneal wound in order to reach improved clinical endpoints.

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META-ANALYSIS

Intravenous glutamine for severe acute pancreatitis: A meta-analysis

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Abstract

AIM: To evaluate the efficacy of intravenous glutamine on the patients with severe acute pancreatitis (SAP).

METHODS: The Cochrane Library, PubMed, EMBASE, and EBM review databases were searched up to June 2012. Randomized controlled trials (RCTs) that compared non-glutamine nutrition with intravenous glutamine supplemented nutrition in patients with SAP were included. A method recommended by the Cochrane Collaboration was used to perform a meta-analysis of those RCTs.

RESULTS: Four RCTs involving a total of 190 participants were included. Analysis of these RCTs revealed the presence of statistical homogeneity among them. Results showed that glutamine dipeptide has a positive effect in reducing the mortality rate (OR = 0.26, 95%CI: 0.09-0.73, P = 0.01), length of hospital stay (weighted mean difference = -4.85, 95%CI: 6.67--3.03, P < 0.001), and the rate of complications (OR = 0.41, 95%CI: 0.22-0.78, P = 0.006). No serious adverse effects were found.

CONCLUSION: Current best evidence demonstrates that glutamine is effective for SAP. Further high quality trials are required and parameters of nutritional condition and hospital cost should be considered in future RCTs with sufficient size and rigorous design.

Key words: Glutamine; Severe acute pancreatitis; Meta-analysis

Core tip: Glutamine dipeptide was given to patients with severe acute pancreatitis (SAP) in order to improve their nitrogen balance and immunonutrition. This meta-analysis aims to enhance our understanding of the clinical and economical validity of glutamine dipeptide for patients with SAP. We report the meta-analysis of four randomized controlled trials involving a total of 190 participants. Results showed that glutamine dipeptide has a positive effect in reducing the mortality rate, length of hospital stay, and the rate of complications. No serious adverse effects were found.

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INTRODUCTION

Acute pancreatitis is a common and sometimes fatal disease that places a significant financial burden on society[1,2]. The mortality rate ranges from 10% to 15% in patients who are diagnosed with severe acute pancreatitis (SAP)[1,3]. The use of enteral nutrition (EN) for SAP was associated with a significant reduction in infectious morbidity, mortality, hospital length of stay, and a trend toward reduced organ failure morbidity[4]. However, the most common

complications of enteral feeding is diarrhea, which can be detected up to 20%-30% of patients. Thus, parenteral nutrition (PN) is still a choice for the patients suffering from the SAP initially.

Glutamine (Gln) is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance. Gln is also a primary fuel for rapidly dividing cells such as enterocytes and lymphocytes, which protect mucosa barrier and enhance immune functions[5]. The results of previous studies have shown that glutamine-enriched total PN (TPN) formulas improve the prognosis of acute pancreatitis[6,7]. It was given to patients with SAP in order to improve their nitrogen balance and immunonutrition[8-11]. Therefore, it is worth knowing whether routine supplementation of glutamine dipeptide is benefit for clinical outcomes. This meta-analysis aims to enhance our understanding of the clinical and economical validity of glutamine dipeptide for patients with SAP.

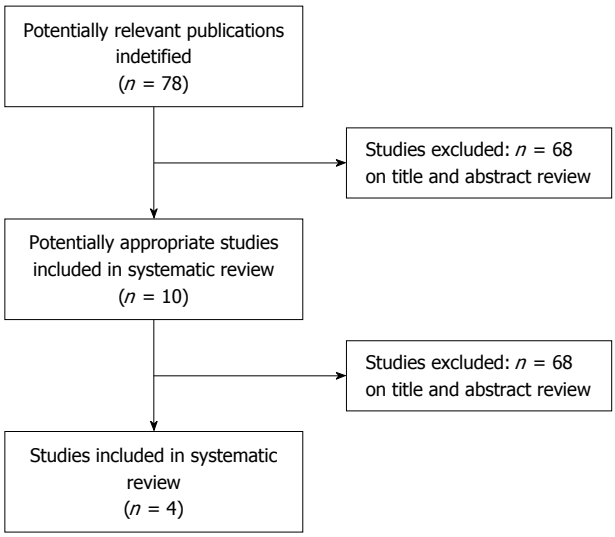

Figure 1 Flow diagram of the study selection process.

MATERIALS AND METHODS

Study selection criteria

The titles and abstracts of all citations identified by the literature search were reviewed. Selection criteria were then applied to all potentially relevant studies. The meta-analysis included clinical randomized controlled trials (RCTs) of patients with SAP. The trials compared standard isonitrogen PN (or EN) and PN (or EN) intravenously supplemented with glutamine dipeptide. Editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Library (Issue 1 2012), PubMed (June 2012), EMBASE (June 2012), and CBM (Chinese Biomedical Literature Database). The query was constructed by using the combination of the following keywords: (SAP or acute pancreatitis) and (glutamine or glutamine dipeptide). Articles published in any language were considered. Abstracts of the articles selected from each of these multiple searches were reviewed and those meeting the criteria were recorded. In the case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used.

Data collection

Data were extracted independently by two reviewers and decided by the research team. The quality of included studies was assessed independently by two authors and discrepancies were resolved by involving the third author. The quality of the studies was assessed using the scores proposed by Cochrane handbook 5 standards: randomization, allocation, concealment, blinding (participants, investigators, outcomes assessors, and data analysis), and completeness of follow-up. The following data were extracted: quantity and group dividing of patients, different doses and days of glutamine dipeptide used, and the baseline of trials. Outcome variables included: mortality rate, length of hospital stay, and rate of complications.

Statistical analysis

The statistical analysis was performed by RevMan5.0 software, which was provided by the Cochrane Collaboration. P value < 0.05 was considered statistically significant. Heterogeneity was checked by the χ^2 test meta-analysis was done with fixed effects model when results of the trials had no heterogeneity. If the results had heterogeneity, random effects model was used and causes were analyzed. The result was expressed with an OR for the categorical variable and weighted mean difference (WMD) for the continuous variables, and with 95%CI.

RESULTS

Search results

There were 78 papers relevant to the searching words. Through the steps of screening the title, reading the abstract and the entire article, only four RCTs involving 190 patients were included (Figure 1). There were three papers published in English and one in Chinese. Data regarding characteristics of the studies, including patients, baseline characteristics and quality assessment of the studies are summarized in Table 1, respectively.

Mortality rate

Four RCTs (involving 190 patients) reported mortality rate. There was no heterogeneity (P = 0.84). Combined analysis indicated that the use of glutamine dipeptide reduced the mortality rate (OR = 0.26, 95%CI: 0.09-0.73, P = 0.01) (Figure 2A).

Length of hospital stay

Three RCTs (involving 130 patients) reported length of hospital stay. There was no heterogeneity (P = 0.77).

Table 1 Characteristics of the studies included in meta-analysis on glutamine dipeptide for severe acute pancreatitis

Study	Hajdú *et al*[8]	Han *et al*[9]	He *et al*[10]	Fuentes-Orozco *et al*[11]
No. of patients included	45	60	41	44
Mean age	No significant difference	No significant difference	No significant difference	No significant difference
Male/female	No significant difference	No significant difference	No significant difference	No significant difference
Body mass index on admission	No significant difference	No significant difference	No significant difference	No significant difference
Plasma glutamine levels on admission	No significant difference	No significant difference	No significant difference	No significant difference
Patients (Gln/Con)	24/21	32/28	20/21	22/22
Gln dipeptide	0.5 g/kg per day, intravenously	20 g/d, intravenously	0.4 g/kg per day, intravenously	0.4 g/kg per day, intravenously
Days of Gln (d) admininistration	7	7	14	10
Randomization	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	Yes	Yes
Double blinding	Yes	Yes	Yes	Yes
ITT analysis	Yes	Yes	Yes	Yes

Gln: Glutamine.

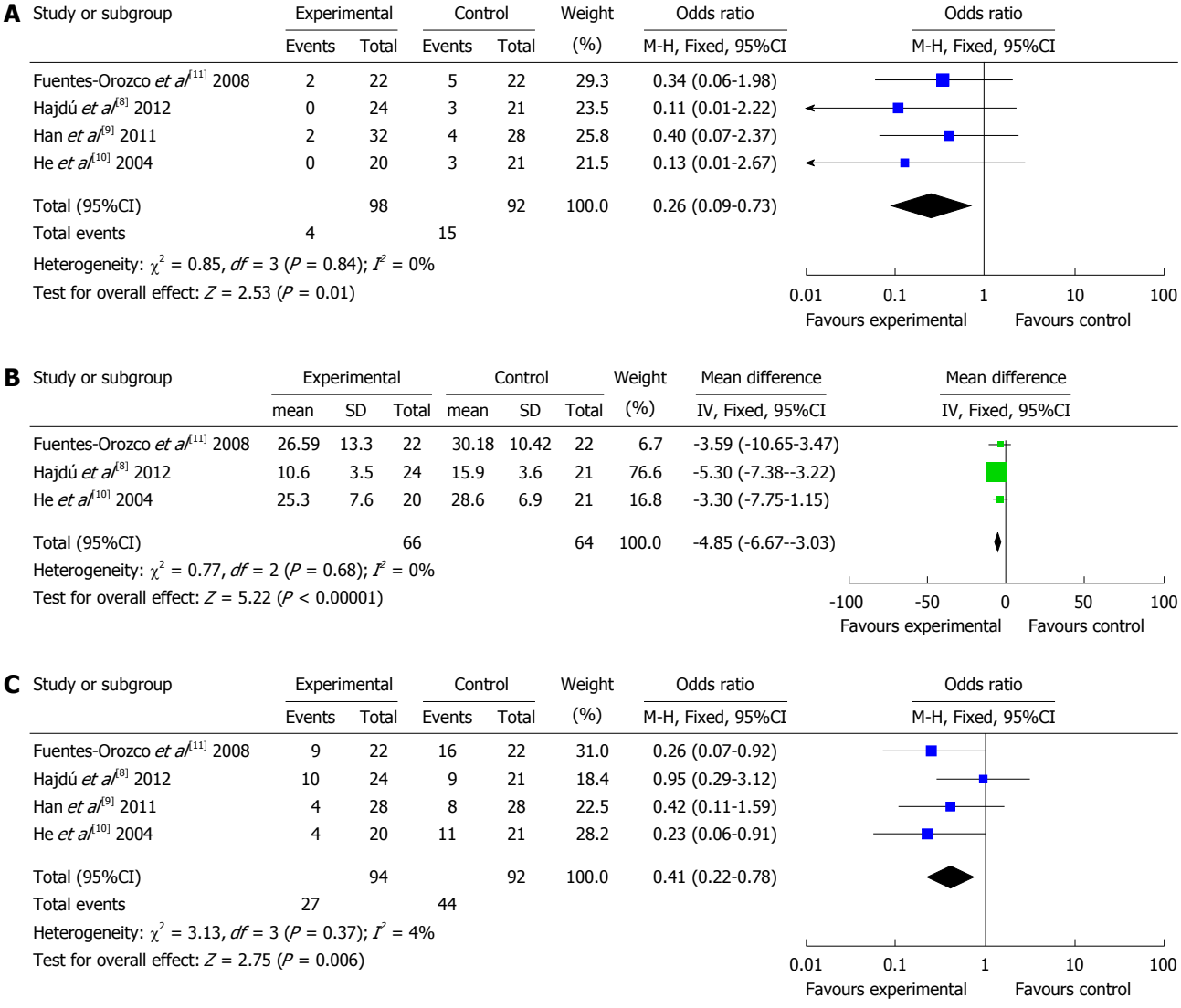

Figure 2 Effect of glutamine dipeptide. A: On mortality for severe acute pancreatitis (SAP); B: On length of hospital stay for SAP; C: On rate of complications for SAP.

Combined analysis indicated that the use of glutamine dipeptide reduced the length of hospital stay (WMD = -4.85, 95%CI: -6.67--3.03, $P < 0.001$) (Figure 2B).

Rate of complications

Four RCTs (involving 190 patients) reported the rate of complications. There was no heterogeneity ($P = 0.37$).

Combined analysis indicated that the use of glutamine dipeptide reduced the rate of complications (OR = 0.41, 95%CI: 0.22-0.78, $P = 0.006$) (Figure 2C).

DISCUSSION

The current meta-analysis demonstrated that the use of glutamine dipeptide could improve the outcome better than standard PN or EN. The use of glutamine dipeptide reduced the mortality rate, length of hospital stay, and the rate of complications. The inclusion criteria of the four RCTs were similar. There was no significant heterogeneity between any of the groups. At the same time, no serious adverse effects were found in all the included studies.

Glutamine is used as a major fuel and nucleotide substrate for rapidly dividing cells such as intestinal mucosal cells and the gut-associated immunocytes[12-14]. Glutamine can prevent atrophy of the intestinal epithelial cells through HSP 70 generation[15] and improve the intestinal immune barrier[16-18]. The deficiency of glutamine is the main cause for protein metabolism disorder, intestinal mucosal injury, enteral wall permeability destruction, bacterial translocation and immunosuppression. All these increase the secondary infection risk and hinder the recovery. A meta-analysis had revealed that glutamine could reduce the infectious morbidity and mortality in critical illness[19]. Another meta-analysis suggested that glutamine dipeptide-supplemented PN was beneficial to postoperative patients by shortening the length of hospital stay and reducing the morbidity of postoperative infectious complications[20].

In the early stage of SAP, the patients tend to be hypermetabolic due to occurrence of SIRS and subsequent multiple organ dysfunction syndromes, resulting in the greatly increased demand for nutrition[21-23]. A study had revealed that plasma glutamine levels were negatively correlated with the severity of acute pancreatitis[24]. The facts that EN is most likely superior to PN in preventing septic complications of acute pancreatitis, it may also eliminate some complications of PN (catheter sepsis, pneumothorax, and thrombosis), and costs less than TPN, make it an increasingly accepted treatment modality. According to the studies enrolled in our analysis, intravenously administered glutamine with TPN is beneficial in the prevention of infectious complications and reduce mortality rate[9-11]. At the same time, the recent RCT revealed that intravenously administered glutamine was able to achieve the same effect with early EN as well[8].

One of the disadvantages of this meta-analysis was that only four RCTs were included. All four studies had high methodological quality and generalizability, nonetheless, there may still have been bias in the final results. Besides, we didn't analyse the parameters of nutritional condition such as concentrations of serum albumin and body weights after the use of glutamine because there is only one RCT has the data. Therefore, more multicenter cooperative studies with prospective design are needed.

In conclusion, PN supplemented glutamine dipeptide with or without EN is effective and safe to reduce the motality rate, occurence of complications, and length of hospital stay in patients with SAP. The encouraging outcomes in this analysis may demonstrate a notion in nutritional supplementation of the patients who are diagnosed with SAP. Further high quality trials are required. Parameters of nutritional condition and hospital cost should be considered in future RCTs with sufficient size and rigorous design.

COMMENTS

Background

Glutamine (Gln) is involved in a wide variety of metabolic and synthetic biochemical processes and acts as nitrogen and ammonium carrier to the liver and kidney. In conditions of excessive demand of Gln during episodes of severe diseases, endogenous Gln production may not be sufficient to meet the increased requirements.

Research frontiers

The results of previous studies have shown that glutamine-enriched total parenteral nutrition formulas improve the prognosis of acute pancreatitis, however, there is no previous meta-analysis confirm the clinical validity and safety of glutamine dipeptide for patients with severe acute pancreatitis (SAP).

Innovations and breakthroughs

Authors performed a meta-analysis of four randomized controlled trials that compared non-glutamine nutrition with intravenous glutamine supplemented nutrition in patients with SAP. Authors' results suggested that parenteral nutrition supplemented glutamine dipeptide with or without enteral nutrition is effective and safe in patients with SAP.

Applications

The encouraging outcomes may demonstrate a notion in nutritional supplementation of the patients who are diagnosed with SAP and provide a practical evidence for the use of Gln.

Terminology

Gln is the most abundant free amino acid in the body and plays a vital role in amino acid transport and nitrogen balance. Deficiency of glutamine increases the secondary infection risk and hinder the recovery. Acute pancreatitis is a common disease with a very varied outcome. Patients with SAP have worse outcomes than those with mild acute pancreatitis. The two major complications of SAP are organ failure and infection, which are both considered as two major reasons for death.

Peer review

This is a well written meta-analysis on the effect of intravenous glutamine in SAP. Mainly the authors systematically summarized and analyzed four randomized trial evidences regarding intravenous glutamine for SAP, and drew the conclusion that glutamine dipeptide has a positive effect in reducing the mortality rate, length of hospital stay, and the rate of complications. No serious adverse effects were found. Therefore the contribution of this meta-analysis is to provide a better knowledge of the benefits of glutamine infusion in SAP.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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