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FIELD OF VISION

Telementoring in education of laparoscopic surgeons: An emerging technology

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Abstract

Laparoscopy, minimally invasive and minimal access surgery with more surgeons performing these advanced procedures. We highlight in the review several key emerging technologies such as the telementoring and virtual reality simulators, that provide a solid ground for delivering surgical education to rural area and allow young surgeons a safety net and confidence while operating on a newly learned technique.

Key words: Telemedicine; Telementoring; Videoconference; Surgical education; Minimal invasive surgery

Core tip: Telemedicine is becoming used more and more in today's surgical practice. We highlight a new low cost telementoring prototype we developed that allows the delivery of better surgical education and delivering specialized expertise to rural areas. Telemedicine is a global term for a computer technology that allows medical information exchange from one location to another *via* telecommunication. Telemedicine helps in eliminating the distance barriers and provides medical expertise to rural communities.

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COMMENTARY ON HOT TOPICS

Telemedicine is a global term for a computer technology that allows medical information exchange from one location to another *via* telecommunication. Telemedicine helps in eliminating the distance barriers and provides medical expertise to rural communities. There are several definitions of telemedicine, but a commonly used definition was proposed by The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): "The practice of medicine and/or teaching of the medical art, without direct physical physician-patient or physician-student interaction, *via* an interactive audio-video communication system employing tele-electronic devices"[1].

Populations around the world are expanding; with the population of the United States of America expected to increase 50% by 2050, yet between 1980 and 2005 there was no increase in medical school enrollments. The funding of all postgraduate positions including

general surgery has not changed significantly in the past 20 years[2]. Unless the rate at which general surgeons are trained increases, the number of general surgeons per population will continue to decline[3]. In 2003, Etzioni *et al*[4] found that as a result of an expanding/aging population, there would be a 31% increase in surgical work between 2001 and 2020. More recently, Williams *et al*[5] estimated that in 2030 there would be a 9% shortage in the general surgical workforce, with greater shortages in other surgical specialties. Due to the future shortage of surgeons, novel ways of surgical education should be explored. Surgical telementoring may be a solution to enhance and improve surgical education.

Surgical technique and technology has rapidly advanced, especially in the areas of laparoscopy. These advanced procedures of minimally invasive and minimal access surgeries are being performed by a greater number of surgeons. Learning to perform a new laparoscopic surgical technique can be extremely challenging, as it relies on the local mentor's knowledge, skill level, and ability to communicate instructions to guide surgical students in their initial experience[6]. Sixty years ago, Gershon-Cohen began to send X-rays using facsimiles over a distance of 28 miles by using simple telephone service to transmit the images[7]. In 1962, DeBakey pioneered the field of telemedicine with the first video conferencing (VC) demonstration of open-heart surgery (Houston, Texas, United States) transmitted overseas *via* satellite, allowing real time viewing of an aortic valve replacement by medical staff in Geneva (Switzerland)[8]. Advances in both communication and computing technologies have allowed the development of a low cost and reliable solution for conveying telemedicine over great distances[2,9,10].

RESEARCH

This paper is a semi systematic review. It is based on a PubMed search as well as the experience from the co-authors who are core researchers at the Norwegian National Centre of Telemedicine in the use of videoconferencing (KAM, HRHP, ROL). The search terms were: Telementoring, tele-mentoring, videoconferencing, video-conferencing. These terms were then combined with the search terms such as laparoscopic surgery and surgical education. Selected key articles and studies were chosen to emphasize the role of videoconferencing and telementoring in surgical education.

The objective of this paper is to explore the use of telementoring in surgical education.

VIDEO CONFERENCING

VC has been in use in medical and surgical fields for many years. In recent years the technology has improved and become more accessible. Today almost every personal computer is able to perform basic videoconferencing at a low cost with relatively high quality.

Needed video conferencing equipment

The International Telecommunication Union (ITU) has defined several technical standards for videoconferencing equipment. ITU defined a standard to establish if the equipment can communicate properly and handle the data load sufficiently. Clear regulations for sound, video, parallel video streams, and data encryption as well patient security, confidentiality, and privacy were set under those standards[11].

Five methods for data transmission during videoconferencing are available today (Table 1): satellite communication, Internet Protocol (IP)-based communication, Integrated Services Digital Network (ISDN), third-generation (3G) and forth-generation (4G/LTE) Mobile phones.

VC in surgical education and postoperative follow-up

VC has been in use among different specialties for many years. Common use of VC is in post-operative treatment and follow-up due to the relatively low costs, advancements in technology and the development of network infrastructures. Reported results of telementoring which is described as a natural fit in surgery[12], are improved surgical practice, education, treatment and postoperative care[13].

Remote presents and telementoring: The RP-7 (RP-7; Intouch Health, Santa Barbara, California) is an example of a high-end robotic remote presence system that can be controlled by a portable personal computer linked *via* Internet connection. Its dimensions are 165 cm in height and 63 cm × 76 cm at its base, comparable in size to that of an average human. The head of the robot is equipped with two advanced digital cameras, audio microphone and sophisticated engineering allows a real-time, two-way audio-video link. In addition the robot is highly maneuverable and allow a wide range of motions, *e.g.*, panning and tilting[10].

Sereno *et al*[14] Described a successful experiment using the previous version of the remote presence robot the RP-6 (predecessor to the RP-7). They have used two type of mentoring methods (1) the standard assistance called "active onsite mentoring" where the expert surgeon provides assistance with verbal instructions and practical support by manipulating or changing the position of instruments and camera when necessary (Figure 1); and (2) "Passive onsite mentoring" where the expert limited his or her support to verbal assistance without using hands to correct the positioning of instruments or camera (a method that is more similar to the one provided by the robot). They concluded that even though "human" mentoring is considered superior over remote "robotic" mentoring, the difference between the two groups was not as large as they had expected. Although it is clear that a remote presence robot may not replace the local mentors, they have been shown that it is a valuable tool in telementoring minimally invasive procedures[14].

Table 1 Technical solutions for data transmission during video-communication[8]

Type of technology used for VC communication	Bandwidth	Pros	Cons	Suitable for	Price
Satellite	⩾ 128 kb/s	Portable Worldwide use (*i.e.*, areas with poor infrastructure)	Price time latency risk of poor video and audio quality	Disasters remote areas	30-35000 USD Worldwide use (*i.e.*, areas with poor infrastructure)
IP-based/internet	Standard ⩾ 768 kb/s	Easy access good quality of video	Varying quality of video dependable on internet traffic	Telementoring follow-up medical education standard VC	50 USD/month - 70 Mbit line Low prices for VC equipment and line rental
ISDN	Normally 3 × 128 kb/s	Reasonably good video quality	Abandoned in the Western world in favor of 3G mobile phone and IP based telephony	Telementoring follow-up medical education	
3G mobile phone	3G mobile phone /modems	64-500 kb/s	Portable rapidly evolving new networks	No data encryption low quality on video poor lens quality Unique mobile standard not compatible with ordinary VC equipment Emergency medicine	30 USD/month for 5Gb data plan Low prices for VC equipment and carrier subscription
4G /LTE	4G mobile phones / modems	299.6 Mbit/s download and up to 75 Mbit/s upload	Varying quality of video dependable on internet traffic	Telementoring follow-up medical education standard VC	

ISDN: Integrated services digital network; VC: Video conferencing.

Figure 1 RP6 robot during laparoscopic telementoring[14].

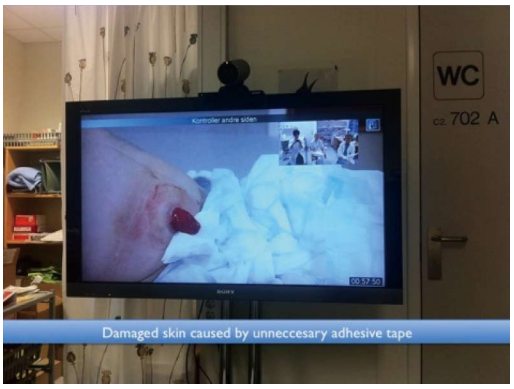

Figure 2 Stoma and post-operative wound care videoconference.

Postoperative follow-up: VC is used as an application for the follow-up of patients during the postoperative period and for outpatient consultation. In our institution, in partnership with the Norwegian Center of Integrated Care and Telemedicine, VC is being used for the follow-up of hemodialysis patients[15], dermatology and orthopedics[8,16,17].

A current RCT for stoma patients and postoperative wound problems is in progress at our institution. Stoma patients are a large and resource-demanding group with most of these patients experiencing long and time consuming travel time to and from our hospital in order to attend follow-up consultations (Figure 2). A specialized nurse is able to conduct an examination of a patient stoma whilst not being within the vicinity of the patient, then guide another nurse located within the vicinity of the patient on how to proceed with the stomas change and follow up. The visual component during the clinical examination is important to assess the stoma and post-operative wound. Early results point toward high patient compliance and satisfaction, reduced costs related to traveling are also recorded. Tele-consultation will therefore be well suited for this patient group[17,18]. We believe that an increased usage of tele-consultation and VC technology will improve the post-operative efficiency as well as reduce the costs associated to post-operative treatments for cancer patients, especially those living in rural areas that have to travel great distances to receive treatment.

TELEMENTORING IN SURGICAL EDUCATION

Telementoring uses similar technological technique of VC. Telementoring permits an expert surgeon, who remains in his/her own hospital, to instruct a non-expert from a peripheral location on how to perform a new laparoscopic technique. The application can be expanded to offer quality control with new or existing procedures[9].

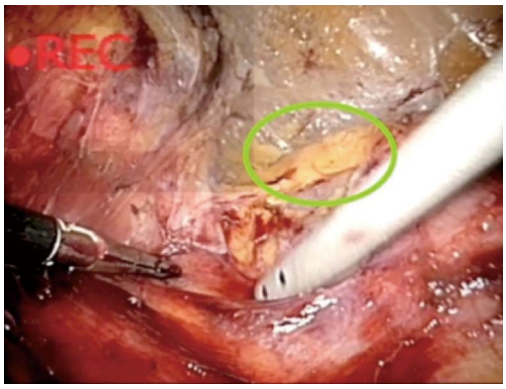

Figure 3 Visual assisted telementoring: enable the mentor to draw lines on a live laparoscopic feed.

Telementoring has been used worldwide, yet in recent years telementoring has been embraced as a viable method to enhance surgical education and has been carried over to the surgical subspecialties. Feasibility studies started in the second half of the 20th century. In the infancy of teleconferencing, Ranshaw *et al*[19] Successfully telementored a rural surgeon in more than 24 cases of laparoscopic herniorrhaphy. All of which were completed successfully. In 2003, telementoring between Brazil and the United States was performed successfully for a laparoscopic bilateral varicocelectomy and percutaneous nephrolithotomy. Over the last 15 years, several studies have shown that telementoring is possible and has positive outcomes.

Telestration technology

Mentoring a surgical resident can be conveyed at several levels: (1) Oral instructions: while watching a transmitted real-time video of the mentee surgeon operating and guiding him using only voice. This method is considered inferior since it depends on the mentor's ability to verbally deliver his instructions accurately so the mentee will understand exactly the intended action; and (2) Visual assisted mentoring: Uses a technology called telestration (Figure 3), this technology has been used mostly in weather forecasts and broadcasted sport events since the early sixties. Telestrators allow surgeons to draw a freehand sketch over the live video stream[20], which enables the mentors to convey their teaching both visually as well as verbally.

Current design limitations: Current existing telestration systems such as the one used in the Da Vinci™. Enables a remote surgeon to point on the local surgeon's display at the master console. However, it does not allow actively drawing lines that would keep their position on the live feed. Telestration however does have the capability as a teaching tool in robotic surgery, yet a proper robotic telemedicine platform does not currently exist[20].

Challenges in laparoscopic surgery training and mentoring

Laparoscopic surgery requires a high degree of special resolution, dexterity, and technical skills. An initial training period is usually required for the majority of surgeons to become expert in these complex techniques by continuous repetition of these tasks. As a result, one would anticipate that to become technically proficient at laparoscopic colorectal resections may require a much longer training period than simpler procedures such as cholecystectomy[21,22]. A number of studies have reported on the length of the learning curve by using different methods and end points over the past 20 years, resulting in suggested numbers between 11 and 110 cases[23,24]. We believe that telementoring can contribute in reducing the learning curve in complex laparoscopic surgeries, however no study has been performed so far to confirm this claim.

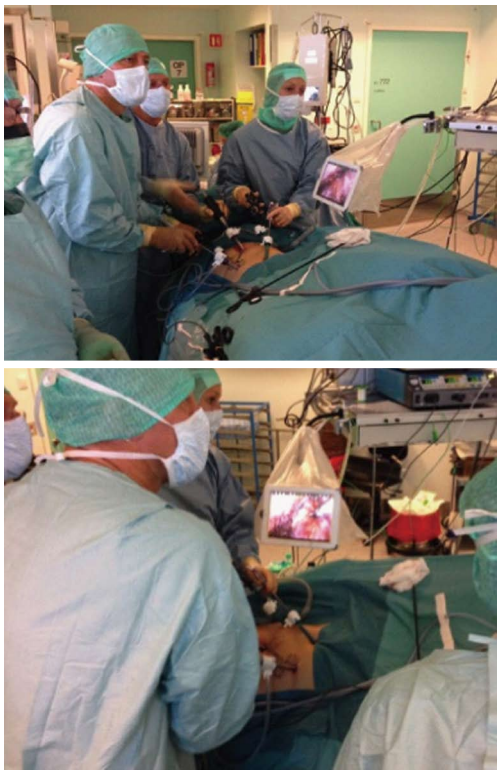

Figure 4 Tablet based mentoring in colorectal surgery at the university hospital UNN Tromsø Norway.

We have conducted several successful pilot experiments at our department with a low cost telementoring prototype based on a common home personal computer and a tablet (Figure 4), with the telementoring performed over regular internet lines. We have developed a unique software and hardware solution that allow us to capture the laparoscopic image directly from the laparoscopic camera and perform several image manipulations in real time. The software we are using provides us with a secure platform that follows and complies with the The Health Insurance Portability and Accountability Act of 1996 Privacy, Security and Breach Notification Rules and regualations(HIPAA). This unique technique is trasferable and repreducable on all laparoscopic disiplenaries *e.g.*, robotic surgery and endoscopy. So far we have con-

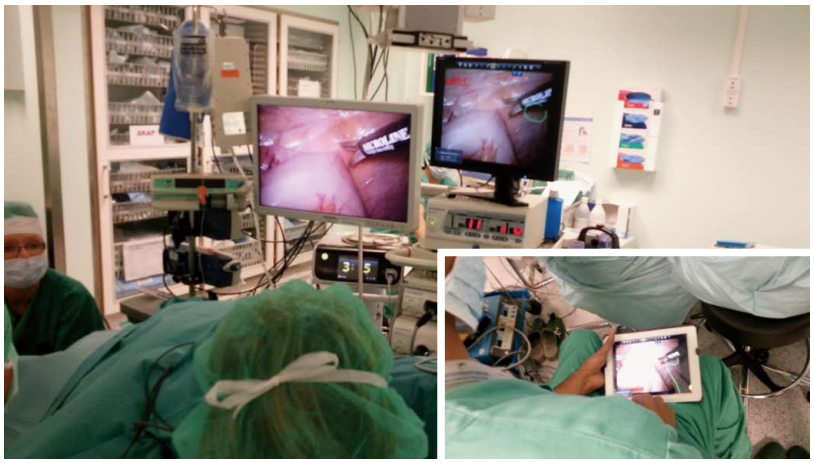

Figure 5 Onsite telementoring in the urology department at the university hospital UNN Tromsø Norway.

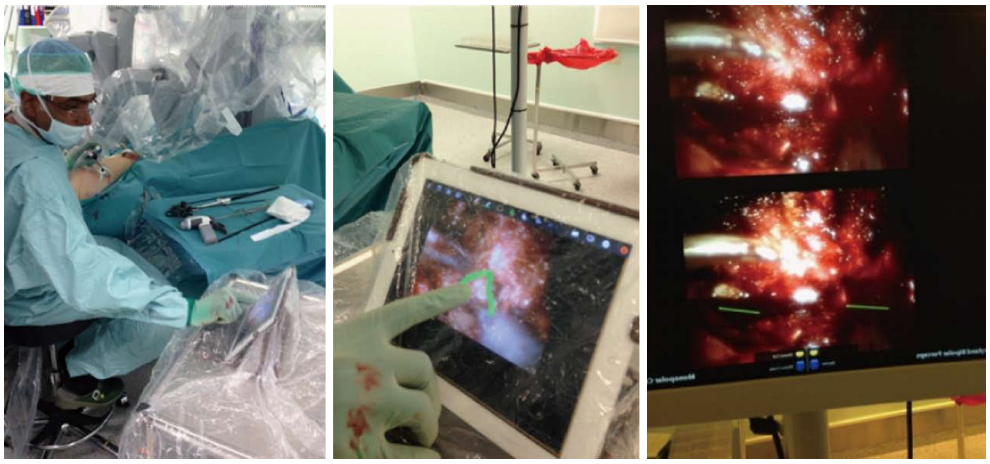

Figure 6 Robotic bedside telementoring using a unique low cost prototype.

ducted successfully in colorectal surgery: abdominoperineal resection and in urological surgery: Adrenectomy, Nephropexy,and Roboitc assisted laparoscopic prostatectomy. Three mentoring methods were used: (1) Active "hands-on" telementoring: the mentor was scrubbed and assisting in the surgery, using the tablet as a tool to enhance his verbal instructions with telestration using the tablet (Figure 4); (2) Passive/on-site mentoring-the mentor was present in the operaitng room but unscrubbed using the tablet to draw illustrations while guiding the mentee surgeons through the operation (Figure 5); and (3) Bed-side mentoring in robotic sugery: the mentor was scrubbed-in and assisting bed-side (Figure 6). All experiments were successful, we are planning in the near future off-site telementoring both short distances and transcontinental.

Telementoring limitations

Networking and Latency: Latency is defined as the amount of time it takes a packet to travel from source to destination; high latency resulted in extreme degradation of performance and has been a major setback in every live videoconferencing session. Telementoring requires a secure high-speed connection with sufficient bandwidth to provide high quality video and audio at both the mentor and mentees station. It has been shown that surgeons are generally able to compensate for delays of up to 700 ms, but delays over 500 ms (half a second) are quite noticeable and potentially detrimental[25]. Mentoring carries inherent limitations and some potential risks. The telementoring process is dependent on primarily the technological adequacy of telecommunication systems; failure of the latter may have clinical implications, which could result in operative errors and the need for conversion.

Cost of generic telementoring systems: The cost of the telementoring system, its software and complete installation (including its secure connection components), ranges from 50000 to 85000 USD. Whereas annual costs for equipment maintenance and broadband services hosting reach approximately 15000 USD[26]. Therefore installation of a telementoring system exclusively for the incorporation of advanced laparoscopic procedures within the setting of a community hospital seems rather unjustified[26]. Evidence exists for cost-effectiveness[27] and safety[28] of telementoring systems, yet there is insufficient data on educational outcomes.

Ethical and legal considerations*:* The physician-patient relationship nowadays has become challenged by

several factors, including technological evolution, novel diagnostic, and treatment modalities. Active involvement of a remote physician in surgery may disturb the therapeutic relationship with the patient and potentially challenge professional collaboration. Prior communication between treating surgeon, the remote mentor, and the patient may need to be included. Matters such as medical liability require a legal framework that would clarify the responsibilities of each part as well as the reliability of the telementoring systems and their integration in routine use. Due to the medical qualifications and licensing in different countries often not being mutually recognized, telementoring projects are currently restricted to national borders[26]. The issue of patient privacy also represents a significant concern and presents a challenge for clinical implementation of telementoring projects. We have been using a HIPPA compliant solution based on a 256-bit encryption (a VPN alternative). This encryption method is considered the best encryption standard existing for civilian medical systems and is relatively inexpensive and not as limited as a standard dedicated VPN-line.

Alternative technologies in surgical education

Virtual reality simulators: Standard surgical training has traditionally been one of apprenticeship, where the surgical trainee learns surgery under the supervision of an experienced and qualified surgeon[29]. Simulation is the replication and modeling of real-life situations for training purposes, such as testing scenario planning and design verification. "Simulation" can be any educational program or technology which removes the live patients from the equation to allow a trainee to learn and master skills in a low-stress, high-feedback environment[30]. The large range of procedures to be learned along with the different learning curves associated with the different procedures raises the problem in which a surgeon experienced in one procedure may not be experienced in another. Therefore the availability of expert surgeons for simulation training might be difficult especially in the periphery[5].

Laparoscopic surgery is different from open surgery because of complex the movements and the need for good hand-eye coordination. The fundamentals of laparoscopic surgery (FLS) box trainer is the gold standard for development of laparoscopic technical skills. However, the scoring metrics require a trained mentor and do not allow for immediate and objective feedback[31]. Virtual reality training is one of the many methods used in laparoscopic surgical training and is currently aimed at improving cognitive, psychomotor and technical skills, of both surgical residents during their studies and for maintaining overall skill of experienced surgeons[32].

Another proven advantage of surgical simulators, virtual reality (VR) simulators in specific, is a routine "warm-up" exercise before "performing" in the operating room. Despite adequate mental preparation, unlike other performers, surgeons do not routinely engage in technical "warm-up" exercises before surgery[33]. The concept of "warm-up" exercises is relatively new and is not applied as standard in today's practice[33]. Short-term practice "warm-up" for 15-20 min with tasks designed to target both psychomotor and cognitive skills that are involved in surgical procedures can greatly enhance skill proficiencies during a the follow-up procedure[34], and is shown to decrease the operative times among experienced surgeons in the operating room[35]. A recent prospective RCT done by Lendvay *et al*[36] Observed significant performance improvement and error reduction rates among surgeons of varying experience after VR warm-up for basic robotic laparoscopic surgical tasks.

Technology limitations: Learning surgical practices with an unrealistic model may lead to a negative training transfer because of the different learning abilities and limitations of the sensory, motor and cognitive system of the trainees. Another disadvantage is the initial setup cost and costs of consumables and maintenance, especially when it is not possible to simulate each and every learning task[30].

The role of computer games in surgical education and training: Minimally invasive operations provide a set of challenges that are not inherent in open operations, such as decreased tactile feedback, the fulcrum effect, and working in a 3-dimensional space while focusing on 2-dimensions. Training residents to be proficient in these specialized skills goes beyond what hands-on experience in the operating room can achieve[37].

Video games have been shown to improve hand-eye coordination, spatial visualization, manual dexterity, and rapid mental processing, which are important in the development of laparoscopic skills[38]. Middleton *et al*[38] Conducted a prospective, single-blinded RCT to determine if playing a computer game over a short duration improved VR surgical simulator performance. Their results, when compared with the control, indicated that the group playing video games significantly improved their simulator performances. Most notable findings included significantly higher scores in accuracy, time to completion, number of left-handed movements, left-handed total path length, and left-handed economy of movement for the hand-eye coordination and bimanual clipping and grasping tasks[38].

Medico-legal aspects of telementoring

The practical aspects of telementoring have not been clarified. Telementoring licensure issues are significant medico legal obstacles in the US but to a lesser degree in Europe. Telementors need to have appropriate privileges from the local hospital where the procedure is performed. During a telementored surgical procedure the primary surgeon, at the operational theatre, has primary medical authority and is the sole responsible surgeon ultimately liable for malpractice during the surgery. The premise is that the mentoring surgeon is providing only recommendations and a professional opinion[6].

CONCLUSION

Remote telementoring is more then just a real-time extension of providing surgical subspecialty advices. It allows young surgeons a safety net and builds confidence while implementing a newly learned technique. Low cost has been one of our primary goals when designing our prototypes for telementoring, in which we managed to have no significant additional expenses. Most operating rooms come replete with laparoscopic equipment, including monitors and a computer with internet capability.

The benefits of telemedicine in the areas of surgical telementoring are potentially large. Remote surgeons/mentors can facilitate procedures that would otherwise not be attempted due to complexity, difficulty, and lack of local surgeon experience. They can also give assistance when unexpected operative findings are discovered and assist in emergencies due to their previous experiences. Developed countries with remote populations such as Australia, United States (Alaska), Canada and Norway are ideal for telesurgical and telementoring technology studies.

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REVIEW

Gastrointestinal endoscopy in the pregnant woman

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Abstract

About 20000 gastrointestinal endoscopies are performed annually in America in pregnant women. Gastrointestinal endoscopy during pregnancy raises the critical issue of fetal safety in addition to patient safety. Endoscopic medications may be potentially abortifacient or teratogenic. Generally, Food and Drug Administration category B or C drugs should be used for endoscopy. Esophagogastroduodenoscopy (EGD) seems to be relatively safe for both mother and fetus based on two retrospective studies of 83 and 60 pregnant patients. The diagnostic yield is about 95% when EGD is performed for gastrointestinal bleeding. EGD indications during pregnancy include acute gastrointestinal bleeding, dysphagia > 1 wk, or endoscopic therapy. Therapeutic EGD is experimental due to scant data, but should be strongly considered for urgent indications such as active bleeding. One study of 48 sigmoidoscopies performed during pregnancy showed relatively favorable fetal outcomes, rare bad fetal outcomes, and bad outcomes linked to very sick mothers. Sigmoidoscopy should be strongly considered for strong indications, including significant acute lower gastrointestinal bleeding, chronic diarrhea, distal colonic stricture, suspected inflammatory bowel disease flare, and potential colonic malignancy. Data on colonoscopy during pregnancy are limited. One study of 20 pregnant patients showed rare poor fetal outcomes. Colonoscopy is generally experimental during pregnancy, but can be considered for strong indications: known colonic mass/stricture, active lower gastrointestinal bleeding, or colonoscopic therapy. Endoscopic retrograde cholangiopancreatography (ERCP) entails fetal risks from fetal radiation exposure. ERCP risks to mother and fetus appear to be acceptable when performed for ERCP therapy, as demonstrated by analysis of nearly 350 cases during pregnancy. Justifiable indications include symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, gallstone pancreatitis, or dilated choledochus. ERCP should be performed by an expert endoscopist, with informed consent about fetal radiation risks, minimizing fetal radiation exposure, and using an attending anesthesiologist. Endoscopy is likely most safe during the second trimester of pregnancy.

Key words: Gastrointestinal endoscopy; Esophagogastroduodenoscopy; Flexible sigmoidoscopy; Colonoscopy; Endoscopic retrograde cholangiopancreatography; Teratogenicity; Endoscopic indications; Endoscopy safety; Endoscopic complications; Pregnancy

Core tip: This article critically analysis the literature on the safety of gastrointestinal endoscopy during pregnancy. Endoscopy is frequently indicated during pregnancy with about 20000 endoscopies performed during pregnancy per annum in America. Although gastrointestinal endoscopy is generally safe in the non-pregnant population the safety of the fetus as well as the patient must be analyzed for endoscopy during pregnancy. This study reviews the literature on the safety of esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, flexible sigmoidoscopy, and colonoscopy during pregnancy and provides guidelines

about the indications, safety precautions, and efficacy of endoscopy during pregnancy.

Friedel D, Stavropoulos S, Iqbal S, Cappell MS. Gastrointestinal endoscopy in the pregnant woman. *World J Gastrointest Endosc* 2014; 6(5): 156-167 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i5/156.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i5.156

INTRODUCTION

Gastrointestinal (GI) endoscopy is a mainstay in the evaluation and treatment of GI symptoms and disorders including abdominal pain, reflux esophagitis, biliary disease, and gastrointestinal hemorrhage. It is usually considered a relatively low risk procedure in the general population that is often performed on outpatients with basic cardiopulmonary monitoring. However, there are unique considerations for endoscopy during pregnancy related to physiological alterations during pregnancy and procedural risks to the fetus in utero (Table 1). The safety of gastrointestinal endoscopy during pregnancy is important because of the commonness of GI symptoms and disorders during pregnancy. About 20000 GI endoscopies are performed annually on pregnant women in America, including > 12000 esophagogastroduodenoscopies (EGDs), > 1000 endoscopic retrograde cholangiopancreatographies (ERCPs), and several thousand sigmoidoscopies or colonoscopies[1]. About 0.4% of all endoscopies are performed during pregnancy[1-3]. The risks during pregnancy to the mother and fetus from common procedures, including upper and lower endoscopy, have not been well validated, and decisions regarding procedure performance are usually made on an individual basis based on professional society guidelines[4]. This work comprehensively, critically reviews the current data and literature on endoscopy during pregnancy; proposes recommendations on endoscopy during pregnancy based on the previously published American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4], with modifications based on new data and consideration of previously unaddressed issues; analyzes how to modify procedures to promote maternal and fetal safety; recommends what to advise patients regarding fetal risks from endoscopy; and aims to stimulate new research in this field to resolve current ambiguities and controversies.

This work reviews relatively common endoscopic procedures including EGD, ERCP, flexible sigmoidoscopy, and colonoscopy, but excludes rare procedures, such as percutaneous endoscopic gastrostomy, pancreatic cyst drainage, and endoscopic therapy for achalasia, which have been recently reviewed[5].

PRE-PROCEDURE EVALUATION AND STABILIZATION

A medical history focused on the GI history, obstetric status, comorbidities, and anesthesiology risks is obtained before scheduling endoscopy during pregnancy. Endoscopy should be scheduled in consultation with an obstetrician. Patients should be medically stabilized before endoscopy, with an endpoint of relatively stable vital signs and relatively normal levels of key serum electrolytes and blood counts. In particular, patients with GI bleeding should receive volume resuscitation, including transfusion of crystalloid or packed erythrocytes as necessary, and should have severe coagulopathy corrected by transfusion of fresh frozen plasma or platelets as necessary. Relative normalization of coagulation parameters is important for successful endoscopic hemostasis.

Patients with active upper GI hemorrhage may undergo nasogastric tube lavage or administration of prokinetic agents, such as parenteral erythromycin, to clear the endoscopic field, potentially shorten procedure time, and decrease intraprocedural aspiration risks[6]. Even though no studies have focused on nasogastric tube insertion during pregnancy for GI bleeding, numerous studies have shown tolerability and safety of nasogastric tube intubation for feeding during pregnancy. These studies demonstrate that nasogastric tube intubation and feeding is generally well tolerated by the mother, with rare and mild maternal complications and with mostly favorable fetal outcomes[7]. Erythromycin is rated by the Food and Drug Administration (FDA) as a category B drug during pregnancy. No evidence of erythromycin teratogenicity was found in a study of 230 child-mother pairs exposed to erythromycin during pregnancy[8]. A large survey of Medicaid recipients in Michigan exposed to erythromycin during pregnancy found minimally or no increased rate of major congenital malformations compared to unexposed controls[9].

Patients are maintained nothing per os (npo) for several hours before EGD or ERCP to avoid intraprocedural aspiration of gastric contents. Patients with ascending cholangitis should receive antibiotic therapy to control sepsis and intravenous fluids as required for hypovolemia before ERCP. Fluid resuscitation is even more important in pregnant patients than in the general population to ensure adequate uterine/fetal perfusion during endoscopy. The patient should be positioned on the left side during endoscopy, if possible, to optimize uterine/fetal perfusion. The patient is administered supplemental oxygen by nasal cannula to optimize uterine/fetal oxygenation. Semi-elective GI endoscopy or GI surgery is optimally scheduled during the second trimester to avoid the highest risk of teratogenesis which occurs during organogenesis during the first trimester and to avoid the highest risk of inducing premature delivery which occurs during the third trimester[4]. Fetal cardiac monitoring should be considered when fetal cardiac sounds become detectable, but few cases of fetal cardiac monitoring have been reported during endoscopy and this monitoring is not considered standard of care[4].

Fetal risks from exposure to endoscopic medications, particularly anesthetics, are an important concern. Nearly 2% of pregnant women receive anesthesia without a sta-

Table 1 Unique features of endoscopy during pregnancy

1 Two or more patients at risk
2 Medications and anesthesia usually used may be contraindicated due to fetal risks
3 Patient position an issue in terms of placental blood flow
4 Greater concerns for blood pressure fluctuations due to concerns about placental perfusion
5 Greater concern for aspiration in later pregnancy
6 Disease states that may be exacerbated by pregnancy (GERD) or specific to pregnancy (hyperemesis gravidarum, gestational diabetes, third trimester liver syndromes-HELLP syndrome, *etc.*)
7 Deferral of procedure to more optimal times (*e.g.*, defer procedure from second trimester to postpartum, with possible expedited delivery)
8 Duration of procedure prime concern
9 Obstetric input and monitoring usually necessary
10 Screening for malignancy and Barrett's esophagus less of a concern
11 Avoidance of radiation-based and interventional ancillary procedures (computed tomography imaging, angiography)
12 Monopolar electrocautery (*e.g.*, with sphincterotomy) may harm fetus

GERD: Gastroesophageal reflux disease.

tistically significant correlation of worse outcomes, other than a trend towards lower neonatal birth weight[10]. The FDA classifies drugs according to fetal safety, including teratogenic and abortifacient potential as follows: Category B drugs are considered relatively safe; category C drugs are likely safe or negligibly harmful; category D drugs are potentially dangerous; and category X drugs are contraindicated during pregnancy (Table 2)[4,9,11]. Generally, category B or C drugs are selected at endoscopy during pregnancy, and category D drugs are avoided unless deemed essential and no safer alternative exists. Medications are more likely to be teratogenic when administered during the first trimester during organogenesis. Attendance of an anesthesiologist is recommended at endoscopy performed during pregnancy to optimize fetal safety of anesthetic drugs. Drugs should be administered at the lowest dosage consistent with good anesthetic practice.

Meperidine (Demerol) is generally felt to be relatively safe during pregnancy (FDA category B), but is increasingly being replaced by short acting narcotics, such as fentanyl, because of faster recovery time. Fentanyl is rated FDA category C during pregnancy. Midazolam is generally preferred over diazepam for endoscopy because it produces transient amnesia in addition to sedation. All benzodiazepines are FDA category D, but midazolam is preferred over diazepam during pregnancy because diazepam was associated with teratogenicity, especially cleft palate malformations, in several, early, small studies[12]. Recent large studies, however, have not shown this association[13,14]. Midazolam has not been associated with cleft palate abnormalities, but might have some potential for fetal injury during the first trimester[15]. Propofol is generally safe during pregnancy (FDA category B). It is generally the anesthetic agent of choice during pregnancy, provided an anesthesiologist is available for administration[4,9-11].

A woman in late pregnancy is best served by endotracheal intubation to prevent aspiration during upper endoscopy. Endotracheal intubation is often advisable during all trimesters of pregnancy for prolonged or invasive procedures, such as therapeutic ERCP, and for patients with active upper GI bleeding, particularly from esophageal varices. A consideration unique to ERCP is teratogenicity from fetal exposure in utero to intraprocedural radiation. This concern restricts ERCP to particularly strong indications, as described below. High risk endoscopies, such as therapeutic ERCP, or low risk endoscopies in high risk patients due to comorbidities or life-threatening indications for endoscopy, should ideally be performed in tertiary medical centers by expert endoscopists where an experienced team of anesthesiologists and obstetricians is available.

When obtaining consent the endoscopist should inform the patient about the potential for fetal complications even though these risks are not believed to be particularly large. The patient should be specifically apprised of fetal risks from radiation exposure if ERCP is contemplated.

Table 2 Fetal risks of endoscopic or peri-endoscopic medications used during pregnancy[1]

Medication class	FDA category of safety in pregnancy	Medications
Proton pump inhibitors	B	Lansoprazole, Pantoprazole, Dexlansoprazole, Esmeprazole, Rebeprazole
	C	Omperazole
Histamine-2 antagonists	B	Cimetidine, Famotidine, Nizatidine, Ranitidine
Antiemetics	B	Odansetron, Metoclopramide, Diphenhydramine, Trimethobenzamide, Prochloropromazine, Doxyamine Succinate and Pyridoxine
	C	Promethazine
Prokinetic agents	B	Metoclopramide, Erythromycin
Anesthesia	B	Propofol, Ketamine
Narcotics	B	Meperidine
	B	Morphine, Fentanyl
Benzodiazepines	D	Diazepam, Midazolam
Reversal agents	B	Nalozone
	C	Flumazenil
Colonic preparations	C	Polyethylene glycol, Phosphate preparations[2]
Antispasmodic	B	Glucagon

[1]FDA categorizations of drug safety during pregnancy accepted as guidelines in the current report and by the American Society for Gastrointestinal Endoscopy (ASGE[4]); [2]This review does not recommend use of phosphate preparations during pregnancy. The ASGE recommends its use "with caution"[4]. FDA: United States Food and Drug Administration.

UPPER ENDOSCOPY

EGD is the most commonly performed endoscopic procedure during pregnancy. Diagnostic EGD is useful for diagnosing gastroesophageal reflux disease (GERD), gastritis, *Helicobacter pylori* (*H. pylori*) infection, peptic ulcer disease, esophageal varices, and malignancy; whereas

Table 3 Indications for esophagogastroduodenoscopy during pregnancy

Strong indications[1]
Dysphagia > 1-2 wk, especially with diminished intake or weight loss
Odynophagia > 1-2 wk
Gross gastrointestinal hemorrhage with hematemesis and/or melena, especially if patient becomes hypotensive, requires blood products, or has a significant acute hemoglobin decline
GI hemorrhage with strong clinical suspicion of varices
Suggestion of malignancy on radiologic imaging studies (*e.g.*, MRI)
Possible gastric outlet obstruction (*e.g.*, from peptic ulcer disease)
Endoscopic therapy for continued UGI bleeding
Balloon dilatation of symptomatic UGI stricture (*e.g.*, endoscopic therapy for reflux stricture)
Moderate indications
Recurrent nausea and emesis (including possible hyperemesis gravidarum) if patient > 16-18 wk pregnant and concern exists for peptic ulcer disease with inadequate patient response to > 2 wk of conservative therapy, including PPI
Strong need for endoscopic placement of enteric tube (*e.g.*, for hyperemesis or severe, prolonged, acute pancreatitis)
Nausea and emesis after UGI surgery (including bariatric surgery) with concern for postsurgical stricture
Weak indications
Hyperemesis gravidarum during first trimester
Self-limited nausea, emesis or abdominal pain
GERD symptoms, excluding dysphagia not responsive to empiric PPI therapy
Routine endoscopic surveillance for higher risk patients (*e.g.*, EGD for personal history of familial polyposis coli)-can be deferred until postpartum
Iron deficiency anemia-should generally be deferred until postpartum

[1]These recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1-4, and 7, but the current report adds recommendations 5, 6 and 8 that were not addressed in the ASGE guidelines. MRI: Magnetic resonance imaging; UGI: Upper gastrointestinal; GERD: Gastroesophageal reflux disease; EGD: Esophagogastroduodenoscopy; PPI: Proton pump inhibitor.

therapeutic EGD is useful for hemostasis of variceal or non-variceal bleeding, dilatation of strictures, and ablation of Barrett's esophagus. Patient position, administered medications, and length of procedure are modest considerations for EGD in the general population, but become critical issues during pregnancy.

EGD appears to be relatively safe for the expectant mother and fetus, though follow-up data is limited. In a case series of 83 pregnant women undergoing EGD, 95% delivered normal infants, and the bad outcomes were uncommon and not clearly related to the EGD but were generally related to high risk pregnancies antecedent to performance of the EGD[16]. Only one maternal complication occurred after EGD: transient pyrexia 12 h after EGD with rapid defervescence without requiring antibiotic therapy and without any source of fever identified by a thorough fever work-up. In an Israeli study, only one fetus died among 60 pregnant females undergoing EGD, and no congenital abnormalities were observed in the 56 live-borne infants, excluding three voluntary abortions[17]. A mailed survey of 3300 gastroenterologists regarding 73 pregnant patients undergoing EGD yielded similarly favorable, pregnancy outcomes[18].

In the study of 83 EGDs during pregnancy, the endoscopic indications were GI hemorrhage in 45%, abdominal pain in 34%, and other in 21%. EGD was diagnostic in 95% of cases performed for acute GI bleeding during pregnancy, similar to the diagnostic yield of EGD in the general population for the same indication[16]. EGD was diagnostic in only about 60% of cases for other indications. The most common diagnosis was reflux esophagitis which occurred in 62%; this high prevalence is explained by increased acid reflux during pregnancy from increased intraabdominal pressure from the enlarged, gravid uterus and decreased LES pressure mediated by gestational hormones[19]. Mallory-Weiss tears occurred in 14%; this relatively high prevalence compared to that in nonpregnant patients is explained by the ubiquity of nausea and emesis during pregnancy. Peptic ulcer was diagnosed in only 14% of cases; this relatively low prevalence compared to that in the general population may be explained by decreased gastric acid secretion during pregnancy mediated by gestational hormones[20]. A low rate of peptic ulcer disease during pregnancy was similarly found in the Israeli study[17].

Nausea and emesis are extremely common during pregnancy. A survey reported 63% of women had nausea and emesis early in pregnancy, and 45% of women had these symptoms late in pregnancy[21]. Extreme cases, associated with paradoxical weight loss despite the pregnancy or electrolyte derangements, are called hyperemesis gravidarum. Two case series reported that endoscopic abnormalities commonly occur in pregnant patients with nausea and emesis, but diagnosis of these endoscopic abnormalities rarely altered patient management beyond instituting proton pump inhibitor therapy[16,17]. This therapy is believed to be relatively safe during pregnancy (all proton pump inhibitors but omeprazole are FDA category B, Table 2), and might reasonably be instituted empirically based on symptomatology without subjecting the patient and fetus to the risks of endoscopy. Although possibly associated with hyperemesis gravidarum, *H. pylori* infection can be reliably diagnosed noninvasively by serum antibodies or stool antigen tests[22]. EGD can therefore be typically deferred for symptoms of hyperemesis gravidarum with administration of empirical therapy comprising antiemetics and proton-pump inhibitors; EGD can be performed in the second trimester or postpartum if symptoms persist. This strategy usually obviates the need for EGD during pregnancy because symptoms of hyperemesis gravidarum typically remit after the twentieth week of pregnancy. Contrariwise, acute gross gastrointestinal hemorrhage manifested by melena, hematemesis, or hypotension, constitutes a strong indication for EGD. Patients with this indication generally have significant endoscopic findings and often require endoscopic therapy[23]. Endoscopy should also be strongly considered when upper GI malignancy is suspected, for dysphagia of recent onset persisting for $\geqslant$ 7 d, or when endoscopic therapy is anticipated (Table 3)[5,14,24].

Variceal hemorrhage is rare during pregnancy be-

cause advanced liver disease decreases fertility, but can occasionally occur in patients with underlying cirrhosis (*e.g.*, mother contracted hepatitis B in utero by vertical transmission) or from development of one of several liver failure syndromes occurring during late pregnancy, such as acute fatty liver of pregnancy. Variceal hemorrhage can, moreover, occur in noncirrhotic patients with hepatic fibrosis or portal vein obstruction because these disorders generally do not impair fertility. Pregnancy exacerbates portal hypertension mostly from gestational increases in plasma volume[25]. Almost one-third of pregnant patients with portal hypertension developed de novo varices during pregnancy, whereas about two-thirds of patients with antecedent varices experience variceal bleeding during pregnancy[26]. Patients administered beta-adrenergic receptor antagonists, such as propranolol, to prophylax against variceal bleeding should be maintained on these drugs during pregnancy. Endoscopic band ligation (EVL) is the preferred initial therapy for esophageal variceal bleeding in the general population[27], but scant published data exists concerning EVL during pregnancy, with only one published case series and about one dozen case reports[28,29]. These limited data show relatively favorable maternal and fetal outcomes of esophageal banding, compared with the poor prognosis in untreated patients[5]. Despite limited current data, endoscopic banding is considered justifiable during pregnancy. Sclerotherapy has been available for decades but is now considered a second-line therapy for variceal bleeding in the general population. The literature on sclerotherapy during pregnancy comprises < 50 patients[5,30]. The main conclusion from the limited literature is that outcomes are best for both the mother and fetus if variceal bleeding is successfully stopped by endoscopy or other interventions[31].

Data on therapeutic EGD for nonvariceal upper GI hemorrhage consist of only 4 patients, including one each of sclerotherapy for bleeding Mallory-Weiss tear, epinephrine injection for esophageal ulcer, thermocoagulation for peptic ulcer with high risk stigmata of recent hemorrhage, and electrocoagulation for duodenal ulcer with high risk stigmata of recent hemorrhage[5]. The bleeding ceased or did not recur in three patients, while the fourth patient experienced continued bleeding after endoscopic therapy that required gastric surgery. All four pregnant patients and their fetuses had favorable outcomes. This extremely limited data on therapeutic endoscopy for hemorrhage from peptic ulcers or Mallory-Weiss tears may suggest good maternal and fetal outcomes provided hemostasis is achieved[5,16]. Although considered experimental during pregnancy due to scant data, endoscopic therapy is justifiable for strong indications, including active bleeding, oozing, and nonbleeding visible vessel. This recommendation is based on expert opinion derived primarily from data on efficacy in nonpregnant patients. The current data are insufficient to recommend specific endoscopic therapies during pregnancy, among the options of banding, hemoclips, sclerotherapy, thermocoagulation, argon plasma coagulation (APC), or electrocoagulation.

Endoscopic electrocoagulation raises special concerns during pregnancy. Amniotic fluid can conduct electricity to the fetus[32]. The grounding pad should, therefore, be positioned to avoid current transmission through the uterus and fetus from the cautery device. Epinephrine is frequently injected during endoscopy to control active GI bleeding in the general population, but may decrease uterine/fetal perfusion and is rated FDA category C drug, with a weak association with teratogenesis during pregnancy[33]. This association may reflect the underlying medical condition for which the epinephrine was administered rather than intrinsic fetal toxicity[9]. Mechanical therapies, such as endoclips or bands, have a theoretical advantage for hemostasis in pregnancy because these therapies avoid fetal exposure to electricity or chemical agents.

Capsule endoscopy is generally considered contraindicated during pregnancy, as reported by the manufacturer, due to no clinical trials performed in pregnant patients[34]. Theoretically, capsule progress through bowel might be retarded in pregnant patients from bowel compression by the enlarged, gravid uterus or from anti-kinetic properties of progestin, a gestational hormone. Only a few cases of capsule endoscopy have been reported during pregnancy, including one case of bleeding from jejunal carcinoid diagnosed by capsule endoscopy and then treated surgically, with ultimate delivery of a healthy infant[35]. Although the reported cases resulted in favorable maternal and fetal outcomes, the current data are insufficient to promulgate clinical guidelines. Capsule endoscopy is currently experimental during pregnancy, but may be considered when extremely strongly indicated, especially when the alternative is gastrointestinal surgery. In providing informed consent, the physician should consider mentioning that pregnancy may theoretically increase the risk of capsule retention.

Deep enteroscopy, including single or double balloon enteroscopy, has not been reported during pregnancy. Pregnancy may theoretically render deep enteroscopy more technically challenging because of compression of bowel lumen and displacement of bowel by the enlarged, gravid uterus. Data are needed to promulgate clinical guidelines regarding safety, efficacy, and indications of deep enteroscopy during pregnancy.

LOWER ENDOSCOPY

Flexible sigmoidoscopy, a relatively simple, quick procedure, usually requires only enema preparation and minimal or no sedation and analgesia. Tap water enemas usually suffice for sigmoidoscopy[4]. Colonoscopy, however, requires more thorough colonic preparation, longer procedure times, and significant sedation and analgesia. Polyethylene glycol preparation has been reported as a preparation for colonoscopy during pregnancy but is inadequately studied in this population. Among 40 women receiving polyethylene glycol for constipation during

pregnancy, 37 had favorable fetal outcomes, and three had poor outcomes: one spontaneous abortion and two very early preterm deliveries[36]. Sodium phosphate preparations have not been studied and should not be used during pregnancy. These current recommendations are stricter than the prior ASGE recommendations to use sodium phosphate "with caution"[4], because of occasional reports of electrolyte abnormalities and even renal failure associated with administration of these preparations to dehydrated nonpregnant patients[37,38].

Despite > 6000 women having indications warranting sigmoidoscopy or colonoscopy per annum during pregnancy[39], only about sixty cases of sigmoidoscopy and only about 40 cases of colonoscopy have been reported during pregnancy[5,40]. Most procedures were performed during the second trimester. The literature likely captures a small fraction of performed procedures. In a study of 46 patients undergoing 48 sigmoidoscopies, after excluding one unknown pregnancy outcome and four voluntary abortions, 38 of the remaining 41 patients delivered healthy infants[40]. Poor pregnancy outcomes included death from prematurity of one live-borne infant, one stillbirth, and one infant with a congenital malformation. All poor outcomes occurred in high risk pregnancies and were not attributed to sigmoidoscopy. Control patients, who were matched for sigmoidoscopy indications but who did not undergo sigmoidoscopy because of the pregnancy, had similar fetal outcomes. Sigmoidoscopy during pregnancy was associated with a high diagnostic yield. Sigmoidoscopy was diagnostic in 59% of the 46 patients. It was significantly more frequently diagnostic when performed for hematochezia than for other indications [22 of 29 (76%) *vs* 5 of 17 (29%), $P < 0.03$ χ^2 test]. Sigmoidoscopic diagnoses among 29 patients with hematochezia included: de novo diagnosis or flares of IBD in 15, acute proctosigmoiditis in 3, bleeding internal hemorrhoids in 2, pseudomembranous colitis in 1, and sigmoid adenoma in 1. Among 17 patients undergoing sigmoidoscopy for other indications diagnoses included: ulcerative colitis in 2, nonspecific colitis/proctitis in 2, and postsurgical anastomotic ulcer in 1. Publication bias of reporting only dramatic cases and treatment bias of performing sigmoidoscopy only for very strong indications may have contributed to the high reported diagnostic yield. The consensus is that sigmoidoscopy is well tolerated during pregnancy with good fetal outcomes in relatively medically stable patients. Sigmoidoscopy should be strongly considered in patients with relatively strong procedure indications, including clinically significant acute lower GI bleeding, refractory chronic diarrhea of unknown etiology, distal colonic stricture, suspected IBD flare, and potential colonic malignancy.

In a study of 20 pregnant patients undergoing colonoscopy, one therapeutic colonoscopy was successfully used to decompress a colon dilated from colonic pseudoobstruction, and colonoscopy was diagnostic in 53% of the 19 remaining colonoscopies[41]. Diagnosed disorders included ulcerative colitis in 5, Crohn's colitis in 2, ischemic colitis in 2, and lymphocytic colitis in 1. Only two mothers developed clinical sequelae temporally associated with colonoscopy; they experienced hypotension which was mild and transient without further clinical sequelae. Fetal outcomes were relatively favorable: 18 healthy infants, one involuntary abortion, and 1 infant born with septum secundum congenital cardiac defect. Study patients undergoing colonoscopy, moreover, had similar or better fetal outcomes than control pregnant patients with the same indications for colonoscopy but who did not undergo colonoscopy because of the pregnancy. In another study of 8 pregnant patients undergoing colonoscopy, pregnancy outcomes included six healthy infants, one voluntary abortion, and one miscarriage four months after colonoscopy[40]. The miscarriage occurred in a mother who experienced a severe flare of ulcerative colitis after self-discontinuing her chronic immunosuppressive therapy. Similar data have been reported in about one dozen individual case reports of colonoscopy during pregnancy: a relatively high diagnostic yield of colonoscopy and a relatively low rate of poor outcomes attributable to colonoscopy[5]. As for sigmoidoscopy, the high diagnostic yield of colonoscopy may reflect publication bias and treatment bias.

Colonoscopy should generally be avoided during pregnancy and be performed only when strongly indicated. Colonoscopy should be considered for the following strong indications: evaluation of a known colonic mass or stricture detected by radiologic examination; active, clinically significant lower GI bleeding; colonoscopic decompression of colonic pseudoobstruction; or other situations to avoid colonic surgery by colonoscopic therapy. These recommendations concur with the published ASGE guidelines[4], except for adding the last two new recommendations. Colonoscopy is not all-or-none and the colonoscopist encountering technical difficulty reaching the cecum or intraprocedural patient intolerance may reasonably abort the colonoscopy without reaching the cecum. Even though the enlarged gravid uterus can compress the colonic lumen and distort normal colonic anatomy, cecal intubation is often achievable at colonoscopy during pregnancy. Reported untoward outcomes in the pregnant mother or fetus are generally related to underlying pathology, such as IBD or colon cancer, rather than the colonoscopy. When necessary, colonoscopy is preferentially performed during the second trimester[4,5,39,40]. Colonoscopy may theoretically be more teratogenic during the first trimester when organogenesis occurs and may theoretically cause more fetal injury in the third trimester by mechanical compression of the enlarged preterm uterus or by neonatal respiratory depression from colonoscopic medications administered just before labor.

Hemorrhoidal bleeding is common during advanced pregnancy because of venous pooling from increased intravascular volume and because of prolonged defecation and increased rectal pressure from increased constipation during pregnancy. Lower endoscopy may often be reasonably deferred during pregnancy for bright red blood per rectum because of this high incidence of hemorrhoidal bleeding during pregnancy and the low incidence

Table 4 Concerns about performance of endoscopic retrograde cholangiopancreatography during pregnancy

1 The procedure is technically challenging
2 The patient is normally placed in prone position for ERCP with consequently decreased placental perfusion for the significant duration of the procedure
3 The patient requires considerable anesthetic medications during ERCP due to discomfort during this particularly prolonged procedure
4 Patients often have preexisting pain and significant acute disease, such as gallstone pancreatitis or cholangitis
5 Fluoroscopy is usually required during ERCP with consequent fetal radiation exposure
6 Complications are more common in ERCP than in other endoscopic procedures and can potentially be severe (*e.g.*, pancreatitis, cholangitis, hemorrhage)
7 Sphincterotomy entails monopolar electrocautery with current possibly traversing the fetus
8 Endoscopic sphincterotomy entails risks of postsphincterotomy bleeding or perforation
9 Repeat procedures may be required, such as ERCP for retained biliary stones or stent malfunction and cholecystectomy for gallstones

ERCP: Endoscopic retrograde cholangiopancreatography.

of colon cancer in this generally relatively young female population. Colon cancer and colonic polyps, however, become a concern in older (> 40 years old) pregnant patients with chronic lower gastrointestinal bleeding[42,43]. Sigmoidoscopy can often reasonably replace colonoscopy to evaluate suspected IBD flares during pregnancy. Polypectomy can usually be deferred until after parturition for small polyps to avoid electricity traversing the fetus because such polyps are unlikely to grow much or become malignant during the interim[4]. However, medium-to-large (> 6 mm in diameter) polyps, polyps displaying high risk features such as multinodularity or central ulceration, or polyps causing lower GI bleeding should likely be removed at an index colonoscopy without deferral until postpartum. Lower endoscopy has been used several times to release an incarcerated, gravid uterus[44]. Sigmoidoscopy should be sufficient to reach this area and relieve the incarceration. Iron deficiency anemia is common during pregnancy due to physiologically increased erythropoiesis. Although colonoscopy is typically indicated to evaluate iron deficiency in the elderly, colonoscopy may generally be reasonably deferred during pregnancy until after delivery for this indication.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY AND ENDOSCOPIC ULTRASOUND

Gastroenterologists are concerned about ERCP during pregnancy (Table 4). The most common indication for ERCP during pregnancy is symptomatic choledocholithiasis, often presenting with jaundice, cholangitis, or gallstone pancreatitis. Pregnancy promotes lithogenesis due to gestational hormones. Estrogen promotes cholesterol synthesis which tends to increase cholesterol saturation of bile, and progesterone decreases gallbladder motility which tends to increase bile stasis[45]. Although cholelithiasis is estimated to have a prevalence of 3%-12% during pregnancy, only 1 per 1000 pregnancies or less are complicated by choledocholithiasis[46]. ERCP is generally the preferred therapy for choledocholithiasis to avoid complex biliary surgery for choledocholithiasis during cholecystectomy[47]. Less common ERCP indications include post-cholecystectomy bile leak, biliary strictures, or pancreatic stents for pancreatic-fluid collections. Menstruating females should be screened by urine or blood tests before ERCP to prevent accidental performance of ERCP during pregnancy with fetal exposure to ionizing radiation. For example, 3 of the 29 patients in one study undergoing ERCP during pregnancy were not known to be pregnant at the time of ERCP and were exposed to ionizing radiation without anticipation or patient discussion about potential fetal consequences[48].

The medical literature includes about 350 cases of ERCP during pregnancy. The individual studies are generally flawed due to small study size, retrospective design, failure to capture all outcomes, and limited follow-up after delivery[5,48-50]. Three retrospective series incorporating > 100 pregnant women, with almost all requiring therapeutic intervention (mostly for choledocholithiasis), imply relatively good outcomes in maternal health status, maintenance of pregnancy, and fetal outcome. These three combined studies were notable for maternal pancreatitis in 5%-16%, one spontaneous abortion 3 mo after ERCP, one fetal demise 26 h after delivery, and prematurity rate of 8%[48-50]. A retrospective study of 65 pregnant patients undergoing ERCP with sphincterotomy similarly reported favorable results[49]. There were 11 maternal complications of pancreatitis, all of which were managed medically without requiring surgery. There were no fetal deaths, perinatal deaths, or congenital malformations among the 59 known fetal outcomes[49]. In the largest prospective study, ten patients underwent biliary stenting for choledocholithiasis, biliary pancreatitis, or retained choledochal stones after cholecystectomy[51]. Cannulation was performed without sphincterotomy by using a guidewire to avoid electrocautery during pregnancy. Nine of ten patients had successful therapy, and the tenth patient underwent repeat ERCP with sphincterotomy and stent placement which was successful. All expectant mothers subsequently did well with births of healthy infants in all cases. One study of 18 patients noted no congenital abnormalities and no developmental defects detected in 11 children followed up until 11 years old[52].

A comprehensive analysis in 2011 of 296 ERCP's during pregnancy with 254 accountable pregnancy outcomes revealed (after excluding 1 voluntary abortion) healthy infants at birth in 237; premature, low-birth weight infants in 11; and bad outcomes of spontaneous abortion or infant death after live birth in 5[5]. The mother experienced post-ERCP pancreatitis in 5%-6%, and post-sphincterotomy hemorrhage in 1%, rates similar to that after ERCP with sphincterotomy in the general popula-

Table 5 Recommendations for endoscopic retrograde cholangiopancreatography during pregnancy[1]

1 Weigh conservative management and/or deferral. Radiation early in gestation is a particular concern. Second trimester may be optimal time
2 Consult with obstetrician
3 Consult with radiation physicist if feasible to calculate appropriate dosimetry
4 Obtain MRCP if useful and available
5 Employ experienced ERCP physician
6 Endoscopic ultrasound may obviate ERCP (if CBD gallstones are not extremely likely)
7 Shield fetus/Employ unit with highly collimated beam/Avoid continuous radiation
8 Employ tactics to minimize/obviate radiation: Aspirate bile/intraductal ultrasound/biliary balloon sweeps w/o fluoroscopy/cholangioscopy/biliary stent placement
9 Avoid taking hard copy radiographs of findings because these use greater amounts of radiation than fluoroscopy
10 Minimize monopolar cautery during sphincterotomy. Employ grounding pad so that electric current does not traverse uterus/fetus

[1]These current recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1,2,5, and 7-10, but the current report adds recommendations 3 and 4 that were not addressed in the ASGE guidelines. ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancrea tography; CBD: Common bile duct.

tion[5,53]. ERCP was deemed beneficial for both mother and fetus for cases of symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, or pancreatitis. Caveats included that ERCP should be performed only if therapy is likely necessary and that the endoscopist should be an expert endoscopist, as technical failures resulted in relatively worse outcomes. A novice endoscopist-in-training should, therefore, not perform ERCP on a pregnant patient, even under supervision by an experienced endoscopist.

Fetal radiation exposure is a major concern for ERCP during pregnancy. Fetal risks are highest during the first trimester during organogenesis when they are considered significant at five rads of exposure[54]. Thresholds are higher and risks are lower during the second and third trimesters. Fetal radiation exposure should be estimated by fetal dosimetry, in which a detection device is placed on the abdomen over the uterus, if the anticipated dose may exceed 10 rads (100 milliGrays)[55]. Radiation exposure is usually considerably less than this amount during ERCP[56]. ERCP without fluoroscopy utilizes aspiration of bile to verify biliary cannulation, but the accuracy of this maneuver is not well validated; only a few, small, clinical series have analyzed this technique[50,57]. Other stratagems can minimize radiation exposure (Table 5), but some fluoroscopy is usually necessary. The endoscopist should minimize fluoroscopy dosage, irradiated area (small field and anterior-posterior projection), and duration by avoiding hard-copy radiographic images in favor of only fluoroscopy, utilizing a medical physicist, using a modern highly-collimated radiation unit, and employing pelvic shielding whenever possible[58].

Endoscopic spyscope (cholangioscopy) enables direct endoscopic visualization of the choledochal and pancreatic ducts. This is useful to confirm complete clearance of stones after balloon sweep or to directly examine or sample focal ductal lesions, including growths or strictures, in the general population. The safety of Spyscope technology is inadequately studied during pregnancy, with only 6 reported cases[50,59]. Although these 6 cases reported favorable maternal outcome, the ultimate fetal outcome was not reported. Direct visualization of bile ducts via cholangioscopy is appealing to confirm ductal clearance, but this maneuver may be time consuming and necessitate copious duct lavage[59]. More studies investigating fetal outcomes are needed to determine fetal safety.

Although the reported studies generally suffer from retrospective study design with only one small prospective study, relatively small numbers of study patients, lack of long term follow-up after birth, and substantial number of unknown fetal outcomes, these studies generally suggest that ERCP should be performed when strongly indicated. Strong indications for ERCP include choledocholithiasis complicated by jaundice, ascending cholangitis, or gallstone pancreatitis; and presentation with abnormal (cholestatic) liver function tests in a patient with gallstones and choledochal dilatation detected by abdominal ultrasound. These recommendations correspond with the published ASGE guidelines[4]. ERCP should not be performed for weak indications, *e.g.*, when therapy is unlikely at ERCP. In such cases MRCP is generally preferred over ERCP because of greater safety in the general population. Clinical studies of ERCP appear to show acceptable small risks to the mother that is comparable to that in the nonpregnant patient, as aforementioned for pancreatitis or post-sphincterotomy hemorrhage, and acceptable fetal risks. The benefits of stone clearance from therapeutic ERCP seem to exceed the fetal risks from performing ERCP during pregnancy. Therapeutic ERCP failed to clear choledocholithiasis in about 10% of reviewed cases. Options after therapeutic ERCP failure include repeat ERCP or surgery.

Conventional trans-abdominal ultrasound is relatively insensitive for choledocholithiasis but MRI/MRCP (magnetic resonance cholangiopancreatography) and endoscopic ultrasound (EUS) are highly accurate, radiation-free modalities to detect choledocholithiasis[60]. MRCP has a very important diagnostic role in directing management of biliary disorders in the general population, but only a couple of studies examined MRCP during pregnancy, with inadequate analysis of fetal safety. One study noted sensitivity was greatest when biliary dilation was detected on prior abdominal ultrasound[61]. In another study, MRCP was used to guide ERCP without radiation[62]. There are scant data on EUS during pregnancy, with about one dozen reported cases[50,63]. There were no maternal complications related to EUS. However, several fetal deaths were reported, which were not temporally related to the EUS and were attributed to the poor medical status of the mother at the time of undergoing EUS,

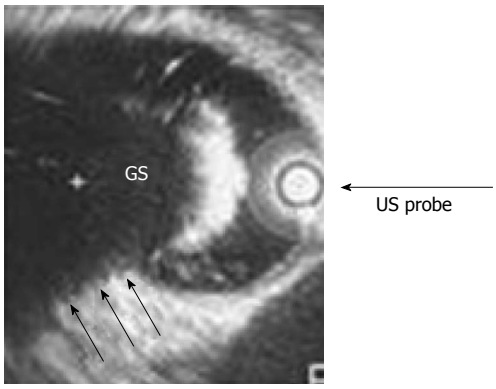

Figure 1 Intraductal ultrasound reveals a gallstone (labeled gallstone) in the common bile duct exhibiting acoustic shadowing (3 parallel arrows) in a middle-aged female patient presenting acutely with right upper quadrant pain, hyperbilirubinemia, and elevated aspartate and alanine aminotransferase levels. During pregnancy, endoscopic ultrasound provides a method to diagnose common bile duct stones without exposing the fetus to the risks of ionizing radiation from endoscopic retrograde cholangiography. US probe: Ultrasound probe; GS: Gallstone.

including recurrent cholangitis or the HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. EUS can help gauge choledochal size and number and size of choledochal stones, but there is concern about the utility of a negative exam, especially when cholelithiasis is present. Intraductal ultrasound may be useful to verify biliary cannulation and duct clearance (Figure 1). The safety of EUS has not been validated during pregnancy, especially regarding fetal outcomes[5].

Tenets of ERCP in pregnancy include: (1) schedule ERCP expeditiously to improve patient and pregnancy outcome (*e.g.*, do not postpone indicated ERCP to second trimester of pregnancy); (2) minimize or eliminate radiation time to reduce fetal exposure; (3) achieve ductal clearance of stones or at least ensure adequate biliary drainage; and (4) facilitate cholecystectomy if necessary. Conservative management of choledocholithiasis is usually unjustified unless, perhaps, very early in pregnancy during organogenesis[64]. Various endoscopic approaches to choledocholithiasis and its complications are reported during pregnancy. Insertion of biliary stents after ductal clearance without sphincterotomy may obviate fetal risks from monopolar cautery, but the stent may become clogged and promote subsequent cholangitis[51]. Performance of both sphincterotomy and biliary stenting still mandates another ERCP that is optimally postponed until postpartum[65]. One group employed nasobiliary drainage, without fluoroscopy, in patients with severe biliary pancreatitis followed by ERCP when the patient stabilized[66].

FUTURE DIRECTIONS

In the future, the burgeoning volume of endoscopies during pregnancy may strengthen the data underlying current guidelines or help formulate modifications. Large studies, preferably prospective, with follow-up of fetal outcome are needed to determine fetal safety of endoscopy. Further data are especially needed on fetal outcome for sigmoidoscopy or colonoscopy performed during pregnancy. The scant data on therapeutic endoscopy must be augmented to determine fetal safety of various techniques of hemostasis including thermocoagulation, electrocoagulation, and APC therapy. "Best practice" recommendations may reduce controversies, such as the optimal approach to symptomatic choledocholithiasis during pregnancy. Combined cholecystectomy and ERCP has not been reported during pregnancy but might become an option[67].

Technology will be emphasized with likely sanctioned use of modalities that have been employed in pregnancy but not recommended due to insufficient data, including MRI, EUS, or capsule endoscopy. Procedures used in the general population, such as unsedated, nasal endoscopy, may be extrapolated to pregnancy. Innovations in capsule endoscopy, such as active propulsion or steering, may prevent capsule retention and thereby render it safer during pregnancy[68]. In particular, colonoscopy with sedation may be replaced by capsule endoscopy without sedation if smaller, steerable capsules are developed. Molecular genetic tests of stool or serum may obviate the need for colonoscopy to evaluate patients for rectal bleeding or colon cancer during pregnancy[69]. New colonoscopic techniques to assess polyp histology before polypectomy, such as narrow band imaging or chromoendoscopy, might help to defer polypectomy of polyps encountered at colonoscopy during pregnancy[70]. Most importantly, new technology may facilitate diagnosis and treatment in pregnancy, such as ultrasound-contrast agents for GI hemorrhage[71], mini-endoscopes, endoscopic glues for hemostasis, and novel mechanical hemostatic devices, such as endoscopic suturing[72]. The new contrast agents for MRCP should be tested in the future regarding safety during pregnancy.

Table 6 Basic principles of endoscopy during pregnancy

1 Weigh benefits of endoscopy versus conservative management
2 Defer endoscopy to second trimester or post-delivery when appropriate
3 Evaluate all proposed medications in terms of teratogenicity and abortifacient potential
4 Obtain consultation from obstetrics and preferably employ anesthesiologist
5 Position patient on left side. Avoid perturbations of blood pressure
6 Minimize drug administration and procedure time
7 For ERCP, minimize or obviate radiation (Table 5). Utilize radiation physicist and calculate dosimetry
8 Utilize bipolar electrocautery. Minimize monopolar use

ERCP: Endoscopic retrograde cholangiopancreatography.

CONCLUSION

Conservatism in performing endoscopy during pregnancy is rational. Endoscopy is usually performed when there is a strong likelihood of significant diagnostic findings and/or endoscopy therapy (*e.g.*, GI hemorrhage, IBD, compli-

cated choledocholithiasis). Patient preparation and physician adherence to general guidelines (Table 6) should help optimize outcomes. There is often multidisciplinary input from obstetricians, perinatologists, and anesthesiologists. Most pregnant women do not sustain untoward effects from endoscopy and the same seems to be the case for the fetus, although long-term follow-up data on subsequently born infants are minimal. More evidence-based guidelines and technological innovations will lessen the ambiguities and challenges in performing endoscopy during pregnancy.

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MINIREVIEWS

Update on gastric varices

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Abstract

Although less common than oesophageal variceal haemorrhage, gastric variceal bleeding remains a serious complication of portal hypertension, with a high associated mortality. In this review we provide an update on the aetiology, classification and management of gastric varices, including acute bleeding, prevention of rebleeding and primary prophylaxis. We describe the optimum management strategies for gastric varices including drug, endoscopic and radiological therapies, focusing on recent published evidence.

Key words: Varices; Gastric; Portal hypertension; Tissue glue; Transjugular intrahepatic portosystemic shunt

Core tip: Endoscopic injection of cyanoacrylate is currently the optimum, evidenced based approach to control active bleeding from gastric varices, apart from bleeding from gastro-oesophageal varice (GOV)-1 which can be treated with variceal band ligation. Transjugular intrahepatic portosystemic shunt (or balloon-occluded retrograde transvenous obliteration in experienced units) can be effective for ongoing bleeding. Cyanoacrylate or transjugular intrahepatic portosystemic shunt can prevent rebleeding from GOV-2 or isolated gastric varice, although variceal band ligation, cyanoacrylate or β-blockers can be used after bleeding from GOV-1. Non-selective β-blockers or cyanoacrylate may be used as primary prophylaxis in patients with known gastric varices, with the choice dependent on clinical and endoscopic findings.

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INTRODUCTION

Gastric varices occur in around 20% of patients with portal hypertension, mostly secondary to liver cirrhosis[1]. Although they bleed less frequently than oesophageal varices, gastric variceal bleeding tends to be more severe with a reported mortality of approximately 45%. In this review, we describe the causes, classification and management of gastric variceal bleeding.

AETIOLOGY AND RISK FACTORS

Pathogenesis of portal hypertension can be secondary to intra-hepatic (*e.g.*, cirrhosis, nodular regenerative hyperplasia), pre-hepatic (*e.g.*, portal or splenic venous obstruction) or post-hepatic (*e.g.*, hepatic venous obstruction) aetiology. Gastric varices can arise due to any of these causes of portal hypertension, but are particularly frequent in patients with splenic or portal venous obstruction.

Risk factors for gastric variceal bleeding include variceal size (large, medium and small defined as > 10 mm, 5-10 mm and < 5 mm respectively), advanced Child's grade of cirrhosis, presence of hepatocellular carcinoma, location of gastric varices (see below) and presence of red spots[1,2].

CLASSIFICATION

Gastric varices are most commonly described using Sarin's classification[1]. This system uses their location in the stomach and their relationship to oesophageal varices. It divides them into gastro-oesophageal varices (GOVs) or isolated gastric varices (IGVs). GOVs are further sub-divided into GOV-1 which extend for 2-5 cm along the lesser curve of the stomach and GOV-2 which extend beyond the gastro-oesophageal junction into the fundus of the stomach. IGVs are sub-divided into IGV-1 located in the fundus and IGV-2 located in the gastric body, antrum or pylorus (Figure 1)[1,3]. Figure 2 shows an endoscopic picture of IGV-1. Hashizume and colleagues also described a classification of gastric varices including their form, location and color, although this is less commonly used[4].

TREATMENT OF ACUTE BLEEDING

Initial management including drug therapy

Variceal haemorrhage should be suspected when a patient with known cirrhosis or evidence of portal hypertension presents with upper gastrointestinal haemorrhage. Volume restitution should be commenced immediately to maintain haemodynamic stability with blood transfusion as necessary aiming for target haemoglobin of 7-8 g/dL[5,6]. A recent Spanish randomized controlled trial showed that in Childs grade A or B cirrhotic patients with oesophageal or gastric variceal bleeding, transfusing below a threshold of 7 g/dL is safe and reduces rebleeding, need for rescue therapy and mortality[6].

Prophylactic antibiotics should be administrated early to patients with suspected or confirmed variceal bleeding as this has been shown to reduce mortality and risk of infection[7,8]. Oral quinolones are often recommended, however the antibiotic choice is often guided by local microbiological advice[5].

Vasoactive drugs should be commenced as soon as possible if variceal bleeding is suspected[5,9]. A meta-analysis comparing emergency sclerotherapy with pharmacologic treatment (including terlipressin, somatostatin or octreotide) for variceal bleeding in cirrhosis showed that vasoactive drugs are beneficial as first-line treatment[10]. However, most patients had oesophageal variceal bleeding. To date, no studies have investigated the use of vasoactive drugs specifically for gastric variceal bleeding. Early endoscopy should be undertaken to confirm the diagnosis and allow endoscopic therapy as required (see below).

Although no formal studies have assessed its use in gastric varices, the temporary use of an intra-gastric balloon such as the Sengstaken-Blackmore tube to tamponade fundal varices may be helpful if bleeding continues despite pharmacologic and endoscopic therapies. This is often used as a bridge to more definitive therapy including placement of a transjugular intrahepatic portosystemic shunt (TIPS; see below)[9,11].

Endoscopic therapies

Endoscopic treatment for gastric variceal bleeding includes endoscopic band ligation, sclerotherapy and endoscopic injection of tissue adhesives or thrombin.

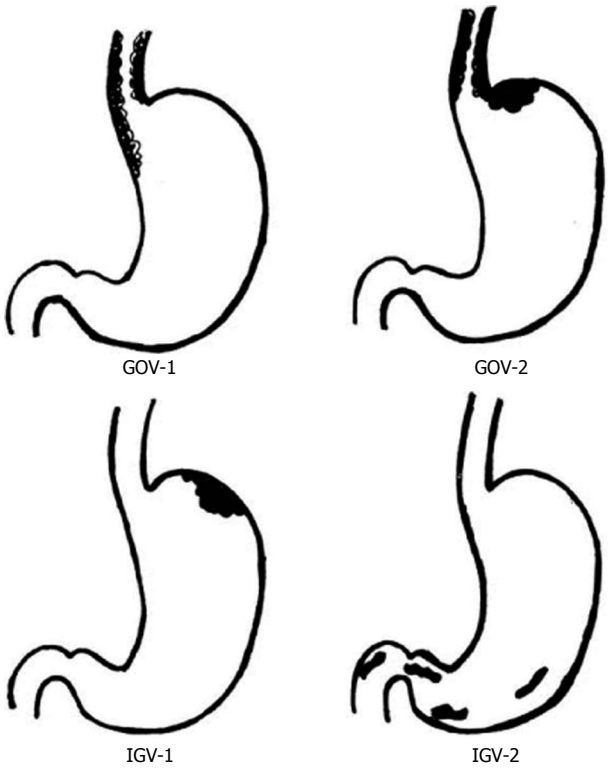

Figure 1 Classification of gastric varices. Available from Sarin *et al*[3]. GOV: Gastro-oesophageal varice; IGV: Isolated gastric varice.

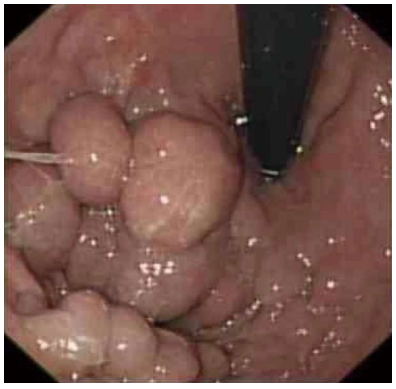

Figure 2 Endoscopic picture of isolated gastric varice-1.

Variceal band ligation: Variceal band ligation is the gold standard for the endoscopic management of oesophageal variceal haemorrhage[5,7], but its role in gastric variceal bleeding is less clear. In a prospective randomized trial by Tan *et al*[12], the efficacy of band ligation to arrest active gastric variceal bleeding in cirrhotic patients was comparable to cyanoacrylate injection, but the rebleeding rate was higher in the banding group. No difference in complications was found between the groups[12].

A study comparing variceal band ligation with the endoscopic use of detachable snares in controlling acute gastric and oesophageal variceal bleeding showed no difference between the two approaches in achieving haemo-

Table 1 Summary of larger and more recent studies using cyanoacrylate for the management of gastric variceal bleeding

Ref.	Type of study	No. of patients (follow-up)	Active bleeding	Haemostasis rate	Rebleeding rate	Complications
Cheng *et al*[19]	Case series	613 (30 mo)	23%	95%	8%	5% "major"
Kang *et al*[15]	Retrospective	127 (18 mo)	38%	98%	23%	3 % "major"
Seewald*et al*[20]	Retrospective	131 (26 mo)	63%	100%	7%	0%
Paik *et al*[14]	Retrospective	121 (12 mo)	26%	91%	13% (at 4 wk)	2% (major complications)
Kind *et al*[21]	Case series	174 (36 mo)	100%	97%	13% "late rebleeding"	8%
Ali-Al *et al*[18]	Retrospective	37 (14 mo)	86%	95%	28%	0 % "major"
Rajoriya*et al*[17]	Retrospective	31 (35 mo)	Not recorded	100%	16%	0 % "major" 6% "minor"

stasis[13]. However variceal recurrence and rebleeding rates were relatively high in both groups. Band ligation is not covered by NICE guidelines for the management of gastric variceal bleeding. However, Baveno V and AASLD guidelines suggest this type of treatment is of particular use in the endoscopic management of bleeding GOV-1, as these are generally considered extensions of oesophageal varices[5,9]. AASLD guidelines also suggest that endoscopic variceal band ligation is an option for patients who bleed from gastric fundal varices if cyanoacrylate is not available[9]. However band ligation is not of proven efficacy for non GOV-1 gastric variceal bleeding.

Sclerotherapy: A study of gastric variceal sclerotherapy with pure alcohol for acute gastric variceal bleeding reported a haemostatic rate of 66%[3]. Gastric variceal sclerotherapy appears more effective in GOV-1 than GOV-2 or IGV-1[3]. However complications associated with the procedure include fever, retrosternal and abdominal pain, dysphagia, rebleeding and ulceration. Similar to the management of oesophageal variceal bleeding, sclerotherapy has been largely replaced by band ligation when appropriate, due to the latter's lower complication and rebleeding rates.

Tissue glues: Cyanoacrylate is a monomer that undergoes rapid polymerization in presence of ionic substances including blood or tissue fluids. Tissue adhesives include histoacryl (N-butyl-cyanoacrylate) and bucrylate (isobutyl -2-cyanoacrylate) and both have been used with success for gastric varices obliteration. A standard forward viewing endoscope is used and the accessory channel and needle catheter are first flushed with lipiodol. The needle is then inserted into the gastric varix and a mixture of lipiodol and tissue adhesive is administered into the varix followed by a flush of saline or sterile water. The needle should be withdrawn immediately to prevent adherence to the varix, then flushed again with saline or sterile water. Injections can be repeated until obliteration of the varices is achieved. Obturation can be confirmed by palpation of the varices using the probe with the needle retracted.

Paik *et al*[14] retrospectively reviewed 121 patients with active or recent gastric variceal bleeding who were treated with N-butyl 2-cyanoacrylate. Bleeding control was achieved in 91% of patients with a 4-wk rebleeding rate of 13%. Fever occurred in 11% of patients and 2% had severe complications attributed to cyanoacrylate embolisms, which however resolved with conservative management. Kang *et al*[15] reported a 98% rate of haemostasis with histoacryl, with few complications. Similar to other studies, fever and abdominal pain were observed, but several uncommon complications were also reported including pulmonary embolism, splenic infarction and adrenal abscess. Case reports of thromboembolic episodes to the pulmonary cerebral and coronary circulation after tissue adhesive injection have also been described[16]. A United Kingdom study achieved an immediate haemostasis rate of 100% with endoscopic histoacryl injection in gastric variceal bleeding[17], and Al-Ali *et al*[18] reported a haemostasis rate of 95% in a Canadian population. Both studies reported no significant complications. A high haemostasis rate of 95% was also reported in a large study performed by Cheng and colleagues[19].

Current evidence of the use of tissue adhesives for gastric variceal bleeding suggests haemostasis control in > 90%. Table 1 summarizes some of the larger and most recent studies using cyanoacrylate for the treatment of gastric varices[14,15,17-21].

A randomized trial of cyanoacrylate injection *vs* TIPS for gastric variceal bleeding showed similar survival and complication rates in both groups, but TIPS was more effective in preventing rebleeding (11% *vs* 38%)[22]. Cyanoacrylate was also compared to TIPS in another two (non-randomised) studies, again with similar haemostasis rates reported between both groups[23,24].

Tissue adhesives appear to be relatively safe and effective in the management of bleeding gastric varices and are generally the endoscopic treatment of choice for bleeding from IGVs and GOV-2. They are recommended by the Baveno V, NICE and AASLD guidelines[5,7,9]. Although there are a few technical issues, appropriate training and use of a unit protocol enable most centers to use it safely and effectively.

Thrombin: Thrombin affects haemostasis by converting fibrinogen to fibrin clot and also influences platelet aggregation[25]. A standard gastroscope is used for the procedure and no specific preparation is required.

Williams *et al*[26] used bovine thrombin for control of gastric variceal bleeding and reported 100% haemostasis with no significant complications and a low rebleeding rate. Ramesh and colleagues also studied bovine thrombin in the management of bleeding gastric varices[27].

Table 2 Summary of studies using thrombin for the management of gastric variceal bleeding

Ref.	Type of thrombin used	No. of patients (follow-up)	Haemostasis	Rebleeding
Williams *et al*[26]	Bovine	11 (9 mo)	100%	27%
Przemioslo *et al*[29]	Bovine	52 (15 mo)	94%	18%
Ramesh *et al*[27]	Bovine	13 (25 mo)	92%	0%
McAvoy *et al*[28]	Human	37 (22 mo)	Not recorded	10.8%

They reported 92% haemostasis in the acute setting, with no rebleeding during follow-up. No patient had an adverse event and no technical problems were encountered. More recent studies have used human rather than bovine thrombin because of the concerns of spongiform encephalopathy.

The largest study to evaluate the efficacy of human thrombin in the management of gastric and ectopic varices bleeding suggests that human thrombin is safe and effective[28]. Thrombin is a promising therapy for bleeding gastric varices but to date no randomized data on its use are available and longer term follow-up is required, therefore more studies are required. Table 2 summarizes some of the largest and more recent studies reporting thrombin use in gastric variceal bleeding[26-29].

Radiologic therapies

Radiologic therapies for gastric varices include TIPS and BRTO (balloon-occluded retrograde transvenous obliteration).

TIPS: TIPS has been well studied in the management of oesophageal varices, with fewer studies undertaken on its use in bleeding gastric varices. An American retrospective comparative study compared TIPS with cyanoacrylate injection for gastric variceal bleeding. No differences were found in survival or rebleeding, but the group treated with TIPS had an increased morbidity requiring prolonged hospitalization because of encephalopathy[23].

Another study compared the clinical outcome of PTFE-coated stent-grafts with bare stents in patients who required emergency or elective TIPS for portal hypertension related complications[30]. During follow-up, 22% of the patients with bare stents had clinically relevant TIPS dysfunction, but no dysfunction was observed in patients treated with coated stent-grafts. Encephalopathy rates were similar. TIPS can also be used if bleeding from gastric varices is not controlled with N-butyl-cyanoacrylate injection, however the portal vein must be patent and careful patient selection is required to minimize risks of encephalopathy[7,31].

Balloon-occluded retrograde transvenous obliteration: Balloon-occluded retrograde transvenous obliteration (BRTO) is a radiologic technique used for the treatment of gastric varices. The right femoral or internal jugular vein is punctured and a balloon catheter is inserted into the left renal vein. After balloon inflation, venography is performed to identify gastric varices, gastrorenal shunts and collateral veins. The veins draining gastric varices are embolised with microcoils and a sclerosant agent is injected until all varices are obliterated.

Hong *et al*[32] compared BRTO with endoscopic injection of cyanoacrylate in the management of acute gastric variceal bleeding and high risk varices (≥ 5 mm with red spots and Child's grade B or C). The haemostasis and rebleeding rates of cyanoacrylate were 100% and 71.4% respectively compared with 76.9% and 15.4% respectively for BRTO. This was a surprising high rate of rebleeding after cyanoacrylate treatment, but included a higher proportion of patients with active bleeding than most studies. Complications were similar. The patients who rebelled were treated with rescue cyanoacrylate or BRTO. These results suggest that BRTO may have a role as rescue therapy in patients with gastric variceal bleeding.

In a small randomized study performed by Choi *et al*[33], BRTO was compared with TIPS for the urgent treatment of active gastric variceal haemorrhage. No differences were found between the groups in immediate haemostasis, rebleeding or encephalopathy. BRTO can be an alternative to TIPS for the management of acute gastric variceal bleeding if gastro-renal shunts are present[33]. However it is rarely performed outside Asian centers[34]. None of AASLD, NICE or Baveno V guidelines specifically recommend BRTO as treatment for gastric varices.

PREVENTION OF REBLEEDING (SECONDARY PROPHYLAXIS)

Therapeutic options for the prevention of gastric variceal rebleeding include use of non-selective β-blockers, repeated endoscopic injection of tissue adhesives, endoscopic band ligation (TIPS, BRTO), surgical intervention and liver transplantation.

Non selective β-blockers

A randomized controlled trial compared endoscopic cyanoacrylate injection with non-selective β-blockers in the secondary prevention of gastric variceal bleeding[35]. Patients with GOV-2 or IGV-1 were included and HVPG measurement was undertaken to assess the response to β-blockade. The cumulative two year survival rates in the cyanoacrylate and β-blocker groups were 90% and 52% respectively, with the difference linked to higher rebleeding in the β-blocker group. The median HVPG in the group treated with β-blockers fell on follow-up but rose in the cyanoacrylate group, which may be attributed to redistribution of blood flow in the portal system after variceal obturation. There was no difference in complication rates.

Another recent randomized controlled trial was reported by Hung *et al*[36] compared repeated gastric variceal obturation with or without non-selective β-blockers in patients with bleeding GOV-2 and IGV-1. The overall mortality and rebleeding rates during follow-up were similar in the two groups although adverse effects were

more common in the combination group. Therefore combining non-selective β-blockers with gastric variceal obturation does not appear to have a role in preventing GOV-2 or IGV-1 rebleeding. However the use of non-selective β-blockers may have a role in GOV-1, similar to the management of oesophageal varices[5].

Endoscopic therapies

Variceal banding: Due to the issues described above, variceal banding is generally only used as secondary prophylaxis for GOV-1 varices, but not for other types of gastric varices.

Tissue adhesives: As noted above, cyanoacrylate injection is significantly more effective than β-blocker treatment for the prevention of rebleeding from gastric varices[35] and has a lower rebleeding rate compared with band ligation in this situation[12]. As stated above, in a randomized study, rebleeding was higher in patients treated with cyanoacrylate compared with TIPS[22]. However both therapies have similar survival, and there are fewer complications with cyanoacrylate which also appears more cost-effective[22-24].

The United Kingdom study reporting long-term results of endoscopic histoacryl injection in gastric variceal bleeding reported a rebleeding rate of 16%. The mean overall follow-up was 35 mo[17]. The Canadian study, with a median follow-up period of 14 mo, reported a late rebleeding rate of 28%[18]. During a follow-up period of 30 mo, 8% of the patients in Cheng's study had recurrent bleeding[19].

Current evidence on the use of tissue adhesives for gastric variceal bleeding report re-bleeding rates of 7%-38%, with relatively few complications (Table 1).

Thrombin: Thrombin seems to be an effective and safe treatment to reduce gastric variceal rebleeding and repeated injections to achieve eradication may not be necessary[25-29]. Reported rates of rebleeding vary from 0-27% (Table 2)[26-29]. As indicated above, more studies are needed to provide comparative data with other treatment modalities before thrombin injection can be routinely used for prevention of gastric variceal rebleeding.

Radiologic therapies

TIPS: Tripathi described TIPS placement in 40 patients with gastric variceal bleeding, 232 with oesophageal, 12 with oesophageal and gastric and 8 with ectopic variceal bleeding[37]. All of the patients had portal hypertension due to parenchymal liver disease. The portal pressure gradient (PPG) before TIPS was lower in the patients with gastric variceal bleeding. Fourteen point seven percent of the patients with oesophageal varices and 20% with gastric varices rebled. Complication rates were similar. Mortality was lower in patients with gastric varices, but only if pre-TIPS PPG was ⩾ 12 mmHg. Most patients who bled after TIPS had a PPG > 7 mmHg suggesting this may be the target to protect against gastric variceal rebleeding. TIPS insertion appears effective for the prevention of gastric variceal rebleeding, although it is more invasive than endoscopic methods, has associated risks of encephalopathy and is not always available[22,30,37].

BRTO: A retrospective study performed by Jang evaluated the clinical outcomes of BRTO for the management of gastric variceal hemorrhage[38]. In 183 patents with confirmed gastric variceal bleeding, BRTO was performed with a technical success of 96.7%, and procedure-related complications occurred in 4.4%. Overall rebleeding rate was 22%.

Cho[39] evaluated clinical outcomes of BRTO in 49 patients who had gastric varices with spontaneous gastrosystemic shunts. Procedural success rate was 83.7% but there were two procedure-related deaths. Other complications included fever, ascites, pleural effusion, portal vein thrombosis, pulmonary thromboembolism and hemoglobinuria. No variceal recurrence or rebleedingwas noted. BRTO can increase PPG, secondary to increased hepatoportal flow and may aggravate pre-existing oesophageal varices and ascites[39,40]. However BRTO is a procedure that preserves hepatic function and can be used in patients with gastric varices and gastrorenal shunts if TIPS is not possible[34].

Use of EUS

The Hong Kong group suggested that patients who undergo EUS-guided cyanoacrylate injection have a significantly lower risk of recurrent bleeding from gastric varices during subsequent follow-up[41]. However others have not confirmed this[17]. There may be a role for ultrasound mini-probes in the future to assess variceal obliteration, but at present this remains an investigative technique.

A new method has been reported for the management of gastric varices with EUS which is a combination of 2-octyl-cyanoacrylate and coils[42]. Thirty patients with acute or recent bleeding from GOV-2 and IGV-1 were treated and use of coils seemed to retain cyanoacrylate with a lower volume required to obliterate varices. Haemostasis was achieved in 100% of patients with a 96% variceal obliteration rate and no procedure related complications. More studies are needed to determine the efficacy of this treatment.

Surgery

Surgical therapies include total shunts, partial (lower diameter) shunts, selective shunts and devascularization procedures. Total shunts control and prevent variceal bleeding but do not improve survival and often precipitate encephalopathy. Selective shunts have lower rates of encephalopathy and are more commonly used[43]. Eighty percent of patients have good control of bleeding and maintenance of portal perfusion with a selective distal splenorenal shunt[44]. Orloff reported that a portal-systemic shunt can be an effective therapy for bleeding varices in patients with portal vein thrombosis and preserved liver function[45]. They reported no recurrent bleeding

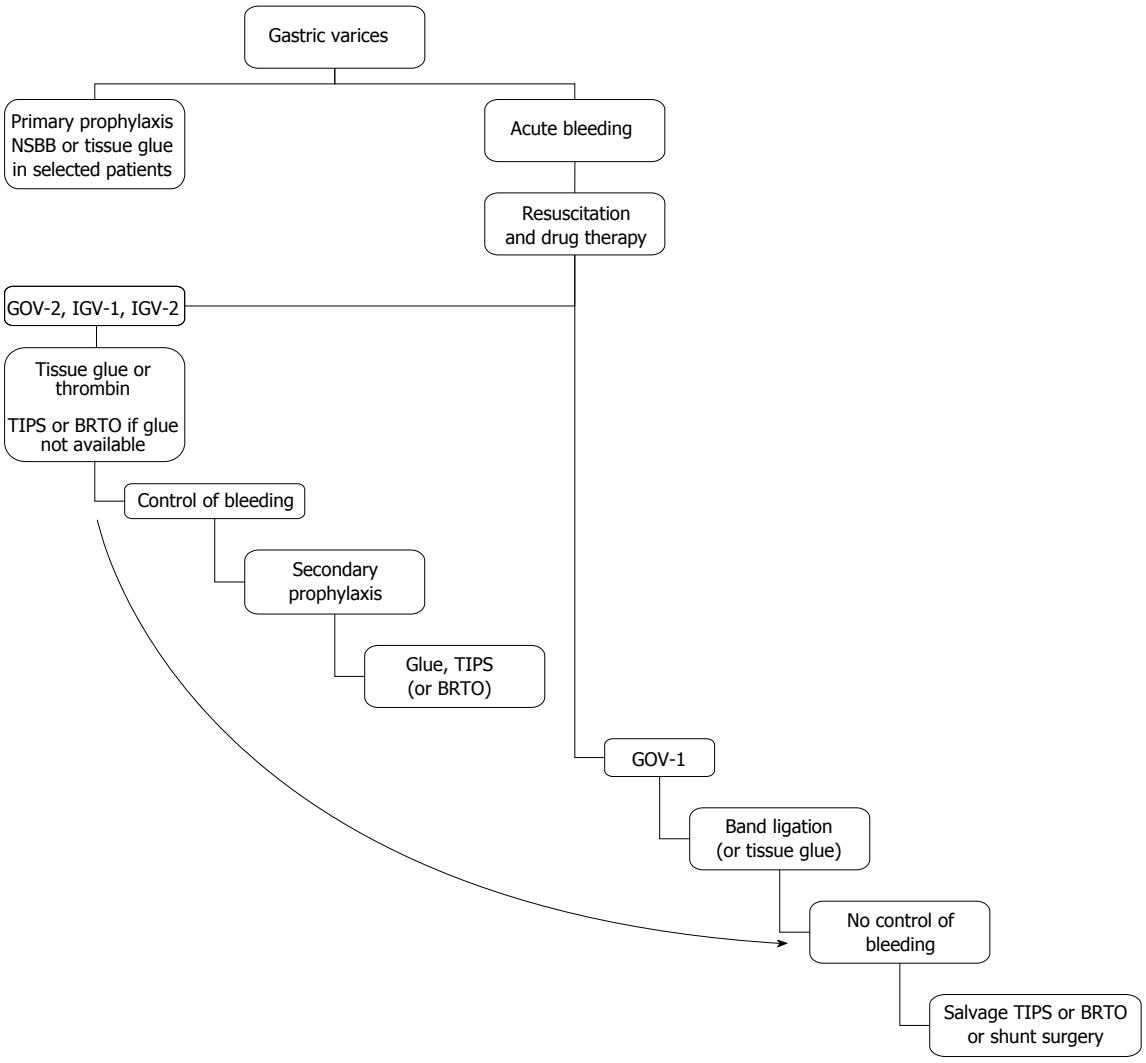

Figure 3 Suggested algorithm for treatment of gastric varices. GOV: Gastro-oesophageal varice; IGV: Isolated gastric varice; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon-occluded retrograde transvenous obliteration.

or encephalopathy and good survival rates. Splenectomy may have a role if there are IGV-1 secondary to an isolated splenic vein thrombosis[9].

Surgery for portal hypertension should be performed by experienced surgeons, in lower risk patients[43]. It is generally considered as rescue therapy, due to the associated risks and the increasing use of simpler endoscopic and radiologic procedures as described above. Liver transplantation should also be considered for eligible patients.

The Baveno V guidelines suggest use of cyanoacrylate or TIPS for the prevention of rebleeding in patients with IGV-1 and GOV-2. The AASLD guidelines consider TIPS as a treatment in patients with recurrent bleeding from fundal varices despite pharmacological and endoscopic therapy.

PRIMARY PROPHYLAXIS

A recent randomized study compared the efficacy of β-blockers, cyanoacrylate injection and no active treatment in the primary prevention of GOV-2 and IGV-1 gastric variceal bleeding[46]. Thirty eight percent, 10% and 53% of the patients bled in the β-blocker, cyanoacrylate and no-treatment groups respectively, over a median follow-up period of 26 mo. The cyanoacrylate group had significantly lower bleeding rates than the other groups for GOV-2, but not for IGV-1 patients. Mortality was significantly lower in the group treated with cyanoacrylate (7%) compared with those given no-treatment (26%) but was not significant compared with the β-blockers group (17%). β-blockers, even if HPVG fell, did not reduce the incidence of first bleeding or mortality. Therefore other factors including high variceal flow or size of gastric varices may be responsible for bleeding.

Kang *et al*[15] retrospectively analyzed patients with cirrhosis and suggested that cyanoacrylate injection is a valuable treatment for gastric varices and also an effective prophylactic treatment for high risk gastric varices.

A retrospective study by Katoh *et al*[47] evaluated the clinical outcomes of BRTO for the treatment of gastric varices. Forty-seven patients were included and it was performed as a primary prophylactic treatment in 40 patients[47]. Technique was successful in 79% with 1 and 5

year survival of 92% and 73% respectively. However this procedure is rarely performed outside Asia. Whilst relatively invasive endoscopic and radiologic procedures may have a future role in the primary prophylaxis of gastric variceal bleeding, more comparative studies are needed.

Despite the paucity of high quality studies assessing primary prophylactic therapy for gastric variceal bleeding, the Baveno V guidelines recommended that patients with gastric varices may be treated with non-selective β-blockers[5]. However these guidelines were published prior to the Indian RCT which suggested a role for cyanoacrylate in this situation[46]. The choice of therapy in this situation may well depend on variceal size, underlying liver function and other clinical factors.

CONCLUSION

Gastric variceal bleeding is a medical emergency with a high mortality. There are relatively few randomized studies assessing management of this condition, therefore guidance on therapy is based on relatively low quality data. However endoscopic injection of tissue glue or thrombin, appear effective in control of bleeding, with TIPS (or BRTO) an option if bleeding continues. To prevent rebleeding from IGV or GOV-2, cyanoacrylate or TIPS is recommended and after bleeding from GOV-1, band ligation, cyanoacrylate, or β-blockers may be used. For primary prophylaxis, patients with gastric varices may be treated with non-selective β-blockers, or possibly cyanoacrylate in selected cases. However further high quality studies are required to help clarify therapeutic strategies in this condition.

A suggested algorithm for the management of gastric varices is shown in Figure 3.

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ORIGINAL ARTICLE

Endocrine cells in the oxyntic mucosa of the stomach in patients with irritable bowel syndrome

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Abstract

AIM: To study the different endocrine cell types in the oxyntic mucosa of patients with irritable bowel syndrome (IBS).

METHODS: Seventy-six patients with IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years), of which 40 also fulfilled the Rome Ⅲ criteria for functional dyspepsia (FDP). Of the entire IBS cohort, 26 had diarrhea as the predominant symptom (IBS-D), 21 had a mixture of diarrhea and constipation (IBS-M), and 29 had constipation as the predominant symptom (IBS-C). Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints served as controls. The patients were asked to complete the Birmingham IBS symptom questionnaire. Both the patients and controls underwent a standard gastroscopy, during which three biopsy samples were taken from the corpus. Sections from these biopsy samples were immunostained using the avidin-biotin complex (ABC) method, for ghrelin, serotonin, somatostatin and histamine. The densities of these cell types and immunoreactivity intensities were quantified using computerized image analysis with Olympus cellSens imaging software (version 1.7).

RESULTS: The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm^2, respectively. There was a significant difference between the tested groups ($P < 0.0001$). Dunn's multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls ($P = 0.03$ and 0.0008, respectively). The ghrelin cell density in patients with both IBS and FDP was 489 (130, 966), and in those with IBS only 490 (130, 956). There was no statistical significant difference between these 2 groups of patients ($P = 0.9$). The immunoreactivity intensity did not differ between any of the groups ($P = 0.6$). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively correlated with ghrelin cell density ($r = 0.65$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = 90.69$; $P < 0.0001$). The densities of the serotonin cells were 63 (51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123) and 40 (0, 46) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. A statistically significant difference was found between the tested groups ($P < 0.0001$). Posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls ($P = 0.02$ and 0.004, respectively), but did not differ in the IBS-total and IBS-M groups from that in controls ($P = 0.5$ and 0.4, respectively). The serotonin cell density

in patients with both IBS and FDP was 62 (25, 115) and in those with IBS only 65 (25, 123). There was no statistically significant difference between these 2 groups of patients (P = 1). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups (P = 0.0.9). The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire (r = 0.56; P < 0.0001) and significantly inversely correlated with that of constipation (r = 0.51; P < 0.0001). The densities of the somatostatin cells were 97 (72, 126), 72 (0, 206), 29 (0, 80), 46 (0, 103) and 206 (194, 314) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). There was a statistically significant difference between the controls and the IBS subgroups (P < 0.0001). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups but higher in IBS-C patients than in the controls (P < 0.01, P = 0.02, and P = 0.0008, respectively). The somatostatin cell density in patients with both IBS and FDP was 86 (0-194), and in those with IBS only 110 (0-206). There was no statistically significant difference between these 2 groups of patients (P = 0.6). There was no significant difference in somatostatin immunoreactivity intensity between the controls. The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density (r = 0.38; P = 0.0007) and was positively correlated with that of constipation (r = 0.64; P < 0.0001).

CONCLUSION: The finding of abnormal endocrine cells in the oxyntic mucosa shows that the endocrine cell disturbances in IBS are not restricted to the intestine. Furthermore, it appears that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the changing stool habits in IBS through their effects on intestinal motility.

Key words: Birmingham irritable bowel syndrome symptom questionnaire; Ghrelin; Immunohistochemistry; Serotonin; Somatostatin

Core tip: There are four endocrine cell types in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells. These cells regulate several functions that are disturbed in patients with irritable bowel syndrome (IBS), such as motility and visceral sensation. Of all these cell types, ghrelin cells are the only endocrine cell type that has been studied in IBS patients. The present study investigated all the oxyntic mucosa endocrine cell types and reported several abnormalities that can shed light on the pathophysiology of IBS.

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INTRODUCTION

The gastrointestinal endocrine cells are scattered among the mucosal epithelial cells lining the gastrointestinal lumen[1-4]. These cells can be divided into several types according to the hormone they produce. They have specialized microvilli that project into the lumen and function as sensors of the luminal contents, and respond by releasing their hormones into the lamina propria, where they act locally (paracrine mode) or *via* the bloodstream (endocrine mode)[5-14]. These cells interact and integrate with each other, with the enteric nervous system, and with afferent and efferent nerve fibers from the autonomic nervous system[1-4]. There are four types of endocrine cell in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells[1,2].

Irritable bowel syndrome (IBS) is a common disorder that affects 10%-20% of the population in the Western world, producing symptoms of abdominal pain/discomfort and altered bowel habits[4]. The findings of laboratory tests, endoscopic examinations and radiological tests are normal in these patients and the diagnosis is based mainly on symptom assessment[4]. Endocrine cell abnormalities have been reported in both the small and large intestines of IBS patients[15-29], but ghrelin cells are the only endocrine cells of the oxyntic mucosa of the stomach that have been investigated thus far[30].

The aim of this study was to determine whether there are abnormalities in the densities and immunoreactivity intensities of all of the endocrine cell types in the oxyntic mucosa of the stomach in a cohort of patients with IBS, including all IBS subtypes: those with diarrhea, constipation or a mixture of both as the predominant symptom (IBS-D, IBS-C and IBS-M, respectively).

MATERIALS AND METHODS

Patients and controls

Seventy-six patients who fulfilled the Rome Ⅲ criteria for IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years)[31,32], of which 40 also fulfilled the Rome Ⅲ criteria for functional dyspepsia (FDP). None of the patients had used proton pump inhibitor medication in the last 6 mo. Of the entire IBS cohort, 26 had IBS-D, 21 had IBS-M, and 29 had IBS-C. All of the patients underwent a complete physical examination and were investigated by way of blood tests to exclude inflammatory, liver, endocrine and any other systemic diseases. Moreover, they were submitted to a colonoscopy with segmental biopsies, which revealed the presence of a normal terminal ileum, colon and rectum in all cases.

Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints were recruited as controls *via* local announcements at our hospitals and in the local newspapers (32 females and 11 males; mean age 40 years, range 20-58 years).

The study was approved by the Regional Committee for Medical and Health Research Ethics West, Bergen, Norway. All subjects provided both oral and written consent to participate.

Symptom assessment

The patients were asked to complete the Birmingham IBS symptom questionnaire, a disease-specific tool for assessing the symptoms of patients with IBS. Its dimensions have good reliability, external validity and sensitivity[33]. The questionnaire comprises 11 questions related to the frequencies of IBS-related symptoms. All of the questions are measured on a 5-point Likert scale. The questionnaire comprises three underlying dimensions: pain, diarrhea and constipation[33].

Gastroscopy, histopathology and immunohistochemistry

Both the patients and controls underwent a standard gastroscopy after an overnight fast, during which three biopsy samples were taken from the corpus (major curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for *Helicobacter pylori* (*H. pylori*) infection (HelicotecUT Plus, Strong Biotech, Taipei, Taiwan). The corpus biopsy samples were fixed overnight in 4% buffered paraformaldehyde, embedded in paraffin, and then sectioned at a thickness of 5 μm. The sections were stained with hematoxylin-eosin and immunostained using the avidin-biotin complex (ABC) method with a VECTASTAIN ABC kit and 3,3'-diaminobenzidine peroxidase substrate (DAB) as the chromogen (Vector Laboratories, Burlingame, CA, United States). The primary antibodies used were monoclonal mouse anti-N-terminus of human ghrelin (code 2016003, Millipore, Temecula, CA, United States), monoclonal mouse antihuman serotonin (clone 5HT-H209, code M0758, Dako, Glostrup, Denmark), polyclonal rabbit antisynthetic cyclic (1-14) somatostatin (code A0566, Dako), and monoclonal mouse antihistamine-hexamethylene diisocyanate-BSA (code 2273835, Millipore). The sections were incubated at room temperature for 2 h with the primary antibodies diluted to 1:200. They were then washed in phosphate-buffered saline (PBS, pH = 7.4) and incubated with biotinylated swine antimouse IgG (in the case of monoclonal antibodies) or goat antirabbit IgG (in the case of polyclonal antibodies), both diluted to 1:200, for 30 min at room temperature. After washing the slides in PBS, the sections were incubated for 30 min with peroxidase-labeled ABC diluted to 1:100, and then immersed in DAB, followed by counterstaining with hematoxylin.

Computerized image analysis

Quantification of the endocrine cells density and immunoreactivity intensity was achieved using Olympus cellSens imaging software (version 1.7). The microscope (BX 43, Olympus, Oslo, Norway) was equipped with built-in Koehler illumination for transmitted light, a light-intensity manager switch, a high-color-reproductivity LED light source, a 6-V/30-W halogen bulb and a digital camera (DP 26, Olympus). The number of immunoreactive cells, the area of epithelial cells, and the immunoreactivity intensity were measured. The number of immunoreactive cells in each field and the area of epithelium were counted manually, while the immunoreactivity intensity in each field was measured using an automatic threshold setting. A × 40 objective was used, which resulted in each frame (field) on the monitor representing a tissue area of 0.035 mm^2. Measurements were made in ten randomly chosen fields in each individual section. Immunostained sections from the IBS patients and controls were coded and mixed, and measurements were made by the same person (M.E.-S.) who was blind to the identity of the patient to whom the tissue sections belonged. The endocrine cell density is expressed as cells/mm^2 epithelium and the immunoreactivity intensity is given in arbitrary units (a.u.).

Statistical analysis

Differences in the gender distribution and the occurrence of *H. pylori* infection between the patients and controls were tested using Fisher's exact test. Differences in the age distribution were tested using the Mann-Whitney nonparametric test. Differences between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Kruskal-Wallis nonparametric test with Dunn's posttest. Correlations were analyzed using Spearman's nonparametric test. The data are presented as median and interquartile (25^{th} and 75^{th} percentile) values and differences with $P < 0.05$ were considered statistically significant.

RESULTS

Patients and controls

The sex and age distributions did not differ significantly between the patients and controls ($P = 0.196$ and $P = 0.360$, respectively). The incidence of *H. pylori* infection did not differ between the patients ($n = 3$) and controls ($n = 2$, $P = 1.0$). The total score for the Birmingham IBS symptom questionnaire for the entire patient cohort (*i.e.*, IBS-total) was 21.5 ± 0.7. The scores on the pain, diarrhea and constipation dimensions were 7.2 ± 0.4, 6.6 ± 0.4, and 7.2 ± 0.4, respectively.

Gastroscopy, histopathology and immunohistochemistry

The esophagus was macroscopically normal while the stomach and duodenum were both macroscopically and microscopically normal in both the patients and controls. Immunoreactive cells were found in the stomach oxyntic mucosa of both the patients and controls, and were either basket or flask-shaped, sometimes with a long basal

Table 1 The densities of different endocrine cell types in controls, IBS-total, IBS-D, IBS-M and IBS-C

Endocrine cell type	Controls	IBS-total	IBS-D	IBS-M	IBS-C
Ghrelin	389 (320, 771)	359 (130, 966)	996 (529, 1154)[a]	358 (120, 966)	126 (0, 262)[c]
Serotonin	63 (51, 82)	51 (25, 115)	120 (69, 128)[a]	74 (47, 123)	40 (0, 46)[b]
Somatostatin	97 (72, 126)	72 (0, 206)	29 (0, 80)[b]	46 (0, 103)[a]	206 (194, 314)[c]

Values are expressed as median and interquartile (25th and 75th). [a]$P < 0.05$, [b]$P < 0.01$ and [c]$P < 0.0001$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

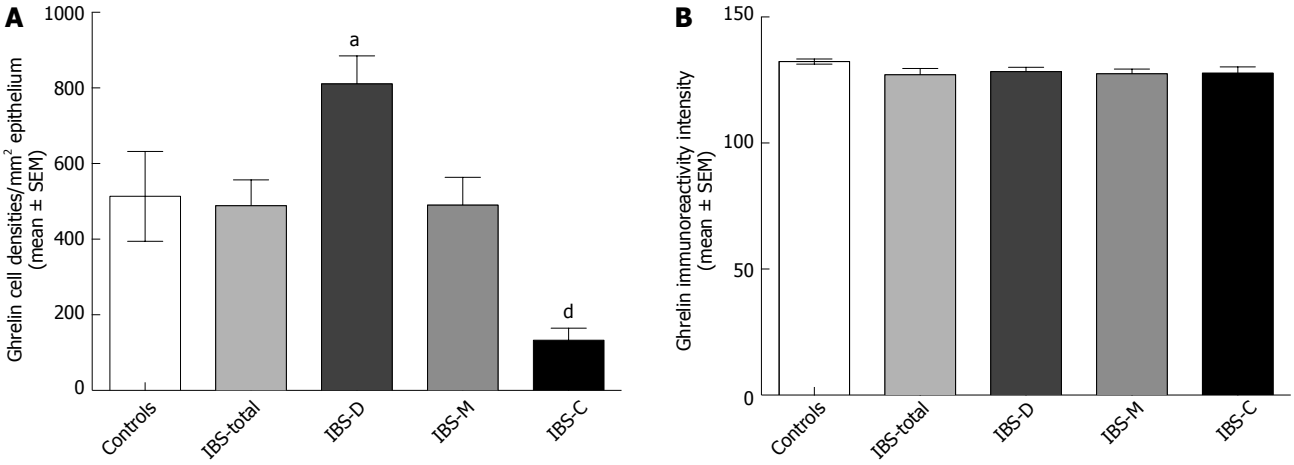

Figure 1 Ghrelin cell densities (A) and ghrelin immunoreactivity intensities (B) in the oxyntic mucosa of the stomach of controls and IBS-total, IBS-D, IBS-M and IBS-C patients. [a]$P < 0.05$, and [d]$P < 0.01$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

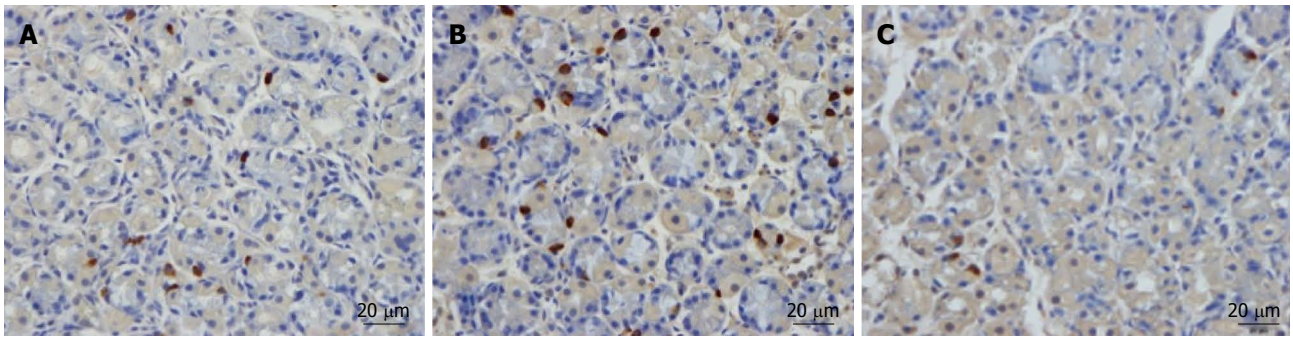

Figure 2 Ghrelin-immunoreactive cells in a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

cytoplasmic process. There were insufficient histamine cells in the biopsy samples studied to allow any reliable quantification thereof.

Computerized image analysis

The results of the quantification of different endocrine cell types in the oxyntic mucosa of the stomach in IBS subtypes are given in Table 1.

Ghrelin: The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm^2, respectively (Figures 1 and 2). The Kruskal-Wallis test revealed a statistically significant difference between the tested groups ($P < 0.0001$). Dunn's multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls ($P = 0.03$ and 0.0008, respectively). The ghrelin cell density in patients with both IBS and FDP was 489.0 ± 68.1, and in those with IBS only 490.1 ± 73.5. There was no statistically significant difference between these 2 groups of patients ($P = 0.9$). The immunoreactivity intensity did not differ between any of the groups, being 133 (131, 134), 131 (125, 133), 129 (125, 133), 132 (124, 134) and 130 (123, 133) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively ($P = 0.6$). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively

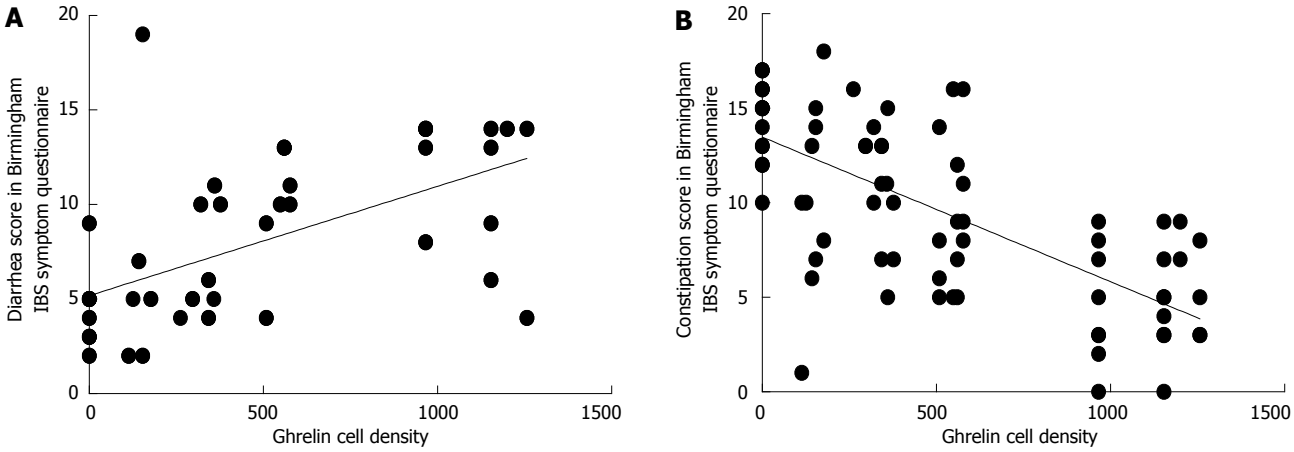

Figure 3 Correlations of ghrelin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

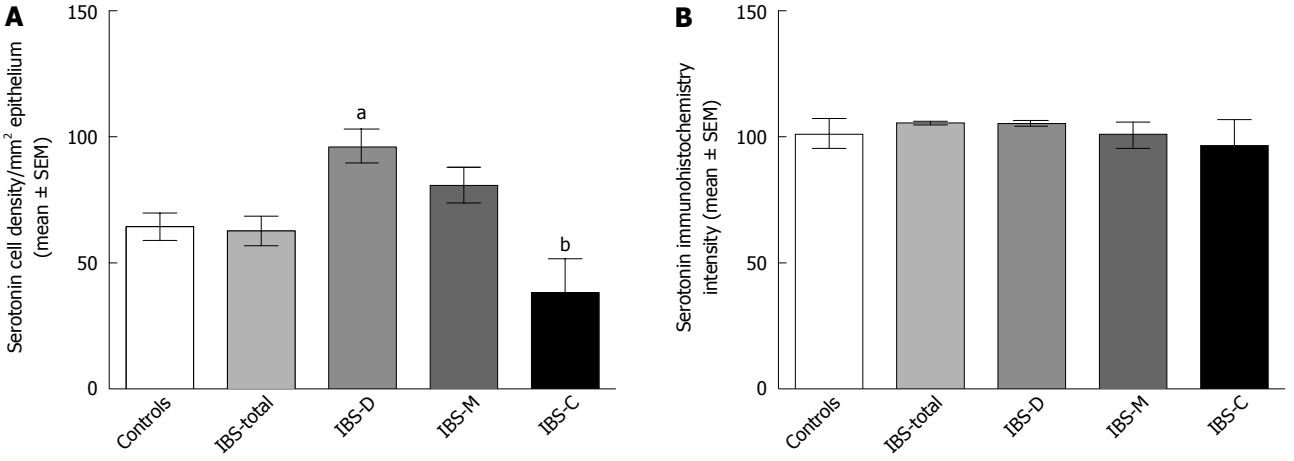

Figure 4 Serotonin cell densities (A) and serotonin immunoreactivity intensities (B) in IBS-total, IBS-D, IBS-M and IBS-C patients. [a]$P < 0.05$, [b]$P < 0.01$ *vs* controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.

correlated with ghrelin cell density ($r = 0.65$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = -0.69$; $P < 0.0001$; Figure 3).

Serotonin: The densities of the serotonin cells were 63 (51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123) and 40 (0, 46) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. The Kruskal-Wallis test revealed a statistically significant difference between the tested groups ($P < 0.0001$). Dunn's posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls ($P = 0.02$ and 0.004, respectively; Figures 4 and 5), but did not differ in the IBS-total and IBS-M groups from that in controls ($P = 0.5$ and 0.4, respectively). The serotonin cell density in patients with both IBS and FDP was 62.0 ± 6.5, and in those with IBS only 65.2 ± 9.5. There was no statistically significant difference between these 2 groups of patients ($P = 1$). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups, being 107 (103, 110), 106 (103, 107), 120 (69, 128), 106 (103, 108) and 107 (101,110) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively ($P = 0.0.9$). The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire ($r = 0.56$; $P < 0.0001$) and significantly inversely correlated with that of constipation ($r = -0.51$; $P < 0.0001$; Figure 6).

Somatostatin: The densities of the somatostatin cells were 97 (72, 126), 72 (0, 206), 29 (0, 80), 46 (0,103) and 206 (194, 314) cells/mm^2 in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). The Kruskal-Wallis test indicated a statistically significant difference between the controls and the IBS subgroups ($P < 0.0001$). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups, but higher in IBS-C patients than in the controls ($P < 0.01$, $P = 0.02$ and $P = 0.0008$, respectively). The somatostatin cell density in patients with both IBS and FDP was 86.3 ± 19.3, and in those with IBS only 110.1 ± 24.1. There was no statistical significantly difference between these 2 groups

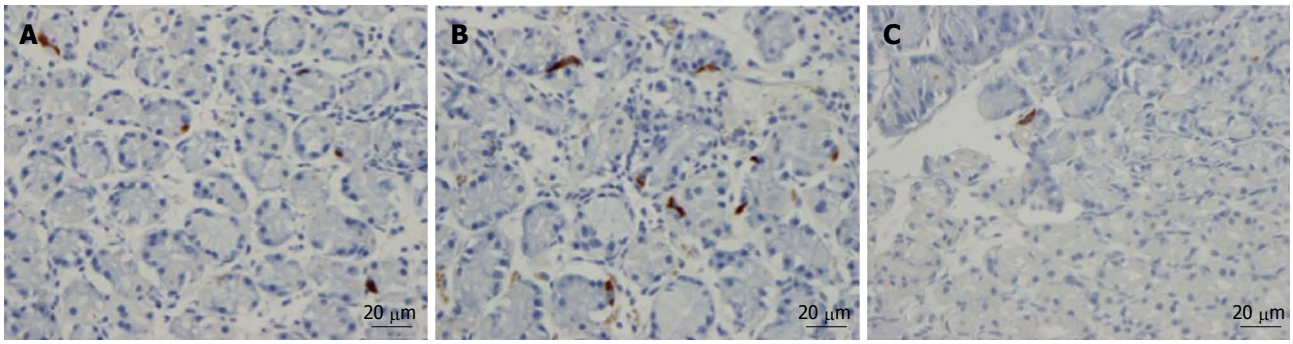

Figure 5 Serotonin cells in the oxyntic mucosa of the stomach of a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

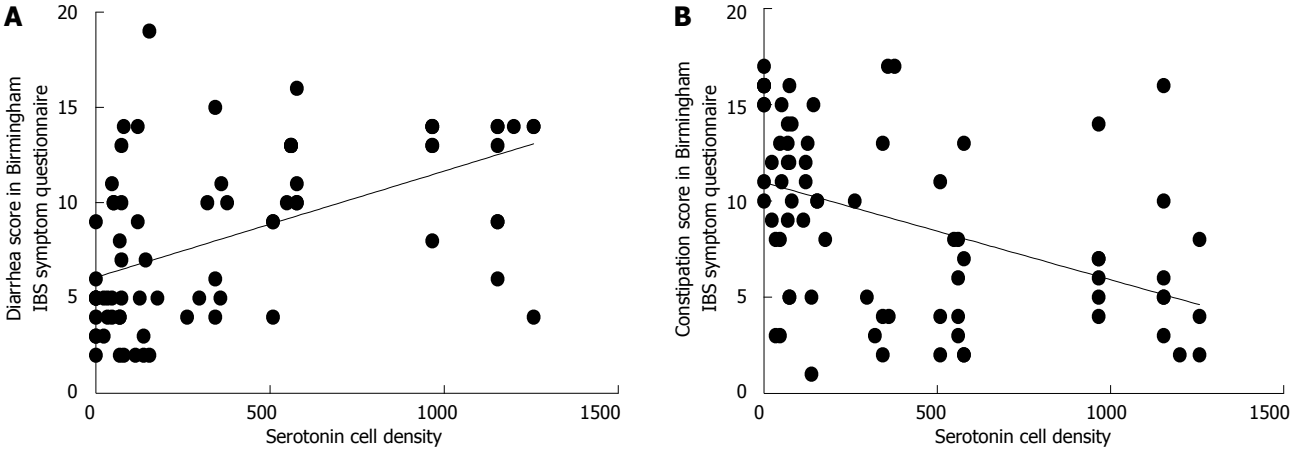

Figure 6 Correlations of serotonin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

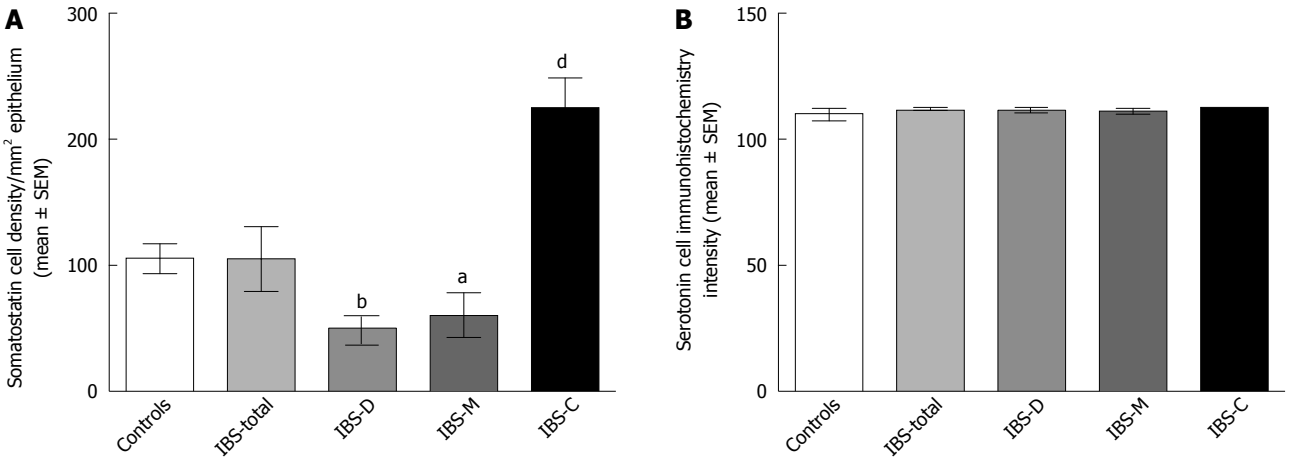

Figure 7 Somatostatin cell densities (A) and somatostatin immunoreactivity intensities (B) in IBS-total, IBS-D, IBS-M and IBS-D patients. The symbols are the same as in Figures 1 and 4. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome. $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{d}P < 0.01$ *vs* controls.

of patients ($P = 0.6$). There was no significant difference in somatostatin immunoreactivity intensity between the controls (111; 109, 113 a.u.) and the IBS-total (112; 111, 112 a.u.), IBS-D (111; 109, 113 a.u.), IBS-M (113; 110, 113 a.u.), and IBS-C (113; 111, 113 a.u.) patients ($P = 0.9$). The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density ($r = -0.38$; $P = 0.0007$) and was positively correlated with that of constipation ($r = 0.64$; $P < 0.0001$; Figure 9).

DISCUSSION

The findings of the present study show that the densities

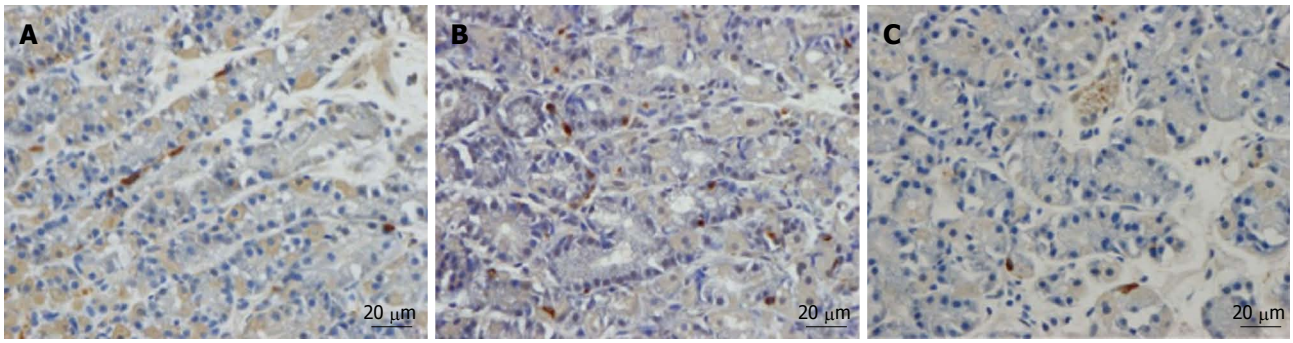

Figure 8 Somatostatin cells in the oxyntic mucosa of the stomach of a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

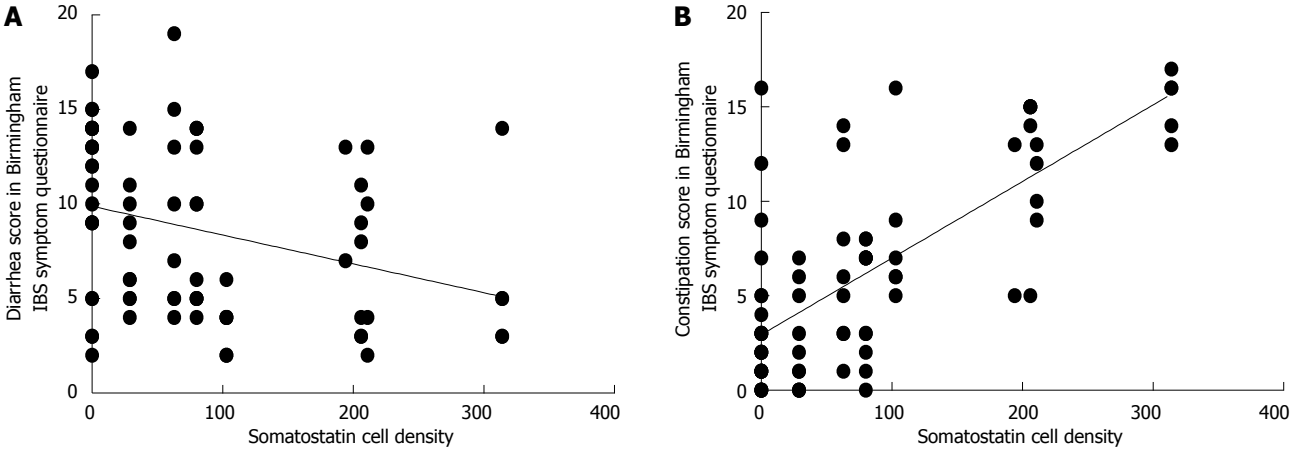

Figure 9 Correlations of somatostatin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.

of the three main types of endocrine cells in the oxyntic mucosa of the stomach, namely ghrelin, serotonin and somatostatin cells, are abnormal in IBS patients. However, the nature of these abnormalities differ with the IBS subtype, whereby the densities of the ghrelin and serotonin cells are high in IBS-D but low in IBS-C, and the density of somatostatin cells is low in IBS-D and IBS-M but high in IBS-C. As there is no difference in the endocrine cells densities between patients with IBS/FDP and patients with IBS only, the abnormalities seen in these cells are most probably caused by IBS. The immunoreactivity intensity of ghrelin, serotonin and somatostatin in IBS patients did not differ from that of controls. This indicates that the cellular content of these hormones in IBS patients is not affected relative to controls, which is an important finding given that the cellular content of a hormone reflects its cellular synthesis and release.

Abnormalities in the endocrine cells in both the small and large intestines have been reported in patients with IBS[15-17,20-30,34,35]. In the small intestine, the duodenal cell densities of gastric inhibitory peptide (GIP), secretin, cholecystokinin (CCK) and somatostatin, and the ileal cell densities of serotonin and peptide YY (PYY) were found to be abnormal[16,18]. In the large intestine, colonic serotonin and PYY, and rectal serotonin, PYY, enteroglucagon and somatostatin cell densities have all been found to be affected[17,19,20]. Postinfectious IBS has been reported to be associated with elevated numbers of duodenal CCK cells and rectal serotonin cells, but decreased numbers of duodenal serotonin cells[15,22,24,26,29,35]. The present observation of abnormal densities of gastric endocrine cells suggests that the endocrine cell disturbances occur throughout the gastrointestinal tract of patients with IBS.

The present findings that ghrelin cell density was high in IBS-D and low in IBS-C confirm the results of an earlier study involving another cohort of IBS patients[30]. The present study also found that the ghrelin cell density was not affected in IBS-M. As well as regulating the release of growth hormone and roles in appetite and energy metabolism[36-39], ghrelin accelerates gastric and small and large intestine motility[40-51]. Ghrelin cell density was found in the present study to be strongly positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. It is thus conceivable that changes in ghrelin cell density play a role in the development of diarrhea and constipation in IBS patients.

Serotonin stimulates colonic motility and accelerates transit through the small and large intestines[52-60]. In the present study, the serotonin cell density was higher in

IBS-D and lower in IBS-C compared to healthy controls and unchanged in IBS-M. Moreover, the serotonin cell density was positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. Therefore, similar to ghrelin, serotonin seems to play a role in the development of both diarrhea and constipation in IBS patients.

Somatostatin inhibits intestinal contraction and gut exocrine and neuroendocrine secretion[2,4]. In the present study, the somatostatin cell density was low in both IBS-D and IBS-M and high in IBS-C. Furthermore, the somatostatin cell density was inversely correlated with the diarrhea score and positively correlated with the constipation score (both assessed by the Birmingham IBS symptom questionnaire). It is therefore possible that changes in the somatostatin cell density also play a considerable role in the development of both diarrhea and constipation in IBS patients.

In conclusion, the results of the present study show that the endocrine cells in the oxyntic mucosa of the stomach in IBS patients are affected and thus that the endocrine cell disturbances observed in IBS are not restricted to the intestine. Furthermore, it appears from the present findings that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the change in stool habits in IBS *via* their effects on intestinal motility. These observations shed light on the pathophysiology of IBS and agonists and/or antagonists to the hormones described can probably be used in the near future in the treatment of patients with IBS.

COMMENTS

Background

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder. The gastrointestinal endocrine cells are localized among the mucosal epithelial cells lining the gastrointestinal lumen. There are four types of endocrine cell in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells. Abnormalities have been reported in both the small and large intestinal endocrine cells of IBS patients. This study was done to determine whether there are abnormalities in the endocrine cell types in the oxyntic mucosa of the stomach in patients with IBS.

Research frontiers

The present study showed for the first time that the densities of three of the four endocrine cell types occurring in the oxyntic mucosa of the stomach were abnormal in IBS patients.

Innovations and breakthroughs

The observation that the endocrine cells of oxyntic mucosa were abnormal shows that the endocrine cell disturbances in IBS are not restricted to the intestine. Hence, IBS is not a large intestine disorder. Moreover, the abnormalities observed in the oxyntic mucosa can explain the gastrointestinal dysmotility seen in IBS patients.

Applications

Based on the observations made in this study, agonists and antagonists for ghrelin, serotonin and somatostatin may be considered for the treatment of IBS.

Peer review

This is an interesting pathological study examining the density of enterochromaffin-like cells in the gastric mucosa of IBS patients. Overall, this study was a lot of work and it adds to the body of literature looking at endocrine cell contribution to the pathogenesis of IBS.

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RETROSPECTIVE STUDY

Withdrawal time in excellent or very poor bowel preparation qualities

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Author contributions: Widjaja D, Bhandari M, Loveday-Laghi V, Glandt M and Balar B contributed equally to this work; Widjaja D, Glandt M and Balar B conceived the study and designed the research; Bhandari M and Loveday-Laghi V gathered the data; Widjaja D and Balar B conducted data analysis; Widjaja D, Bhandari M, Loveday-Laghi V, Glandt M and Balar B prepared, edited and finalized the manuscript.

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Abstract

AIM: To evaluate association(s) between withdrawal time and polyp detection in various bowel preparation qualities.

METHODS: Retrospective cohort analysis of screening colonoscopies performed between January 2005 and June 2011 for patients with average risk of colorectal cancer. Exclusion criteria included patients with a personal history of adenomatous polyps or colon cancer, prior colonic resection, significant family history of colorectal cancer, screening colonoscopy after other abnormal screening tests such as flexible sigmoidoscopy or barium enema, and screening colonoscopies during in-patient care. All procedures were performed or directly supervised by gastroenterologists. Main measurements were number of colonic segments with polyps and total number of colonic polyps.

RESULTS: Multivariate analysis of 8331 colonoscopies showed longer withdrawal time was associated with more colonic segments with polyps in good (adjusted OR = 1.16; 95%CI: 1.13-1.19), fair (OR = 1.13; 95%CI: 1.10-1.17), and poor (OR = 1.18; 95%CI: 1.11-1.26) bowel preparation qualities. A higher number of total polyps was associated with longer withdrawal time in good (OR = 1.15; 95%CI: 1.13-1.18), fair (OR = 1.13; 95%CI: 1.10-1.16), and poor (OR = 1.20; 95%CI: 1.13-1.29) bowel preparation qualities. Longer withdrawal time was not associated with more colonic segments with polyps or greater number of colonic polyps in bowel preparations with excellent (OR = 1.07, 95%CI: 0.99-1.26; OR = 1.11, 95%CI: 0.99-1.24, respectively) and very poor (OR = 1.02, 95%CI: 0.99-1.12; OR = 1.05, 95%CI: 0.99-1.10, respectively) qualities.

CONCLUSION: Longer withdrawal time is not associated with higher polyp number detected in colonoscopies with excellent or very poor bowel preparation quality.

Key words: Bowel preparation quality; Withdrawal time; Polyp detection; Screening colonoscopy

Core tip: This study revealed the merit of a novel finding that longer withdrawal time was not associated with higher polyp number detected in colonoscopies with excellent or very poor bowel preparation quality. The conclusion of this study may change the way we perform screening colonoscopy with excellent or very poor bowel preparation qualities, especially in those with high risk to develop complications related to prolonged sedation.

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INTRODUCTION

Polyp detection rate during colonoscopies is influenced by factors including withdrawal time and quality of bowel preparation[1,2]. Barclay *et al*[1] reported that colonoscopies with longer withdrawal had higher adenoma detection rates. In a similar retrospective study of over 10000 colonoscopies, Simmons *et al*[3] found that prolonged withdrawal time was associated with higher polyp detection rates and that overall median polyp detection corresponded to a withdrawal time of > 6.7 min. In the same publication year, the American College of Gastroenterology and American Society for Gastrointestinal Endoscopy recommend that the average withdrawal time should exceed 6 min in normal colonoscopies in which no polypectomies or biopsies were performed[4]. The strategy of prolonged withdrawal time may logically increase polyp detection rate during colonoscopies with inadequate bowel preparation qualities, which was reported between 23% and 30% in the United States[5-9]. However, since the implementation of this recommendation, quality improvement efforts by simply mandating a minimal withdrawal time have largely proven to be unsuccessful in significantly improving polyp detection rate[10,11].

Although the effect of longer withdrawal time on higher adenoma detection rate was not related to bowel preparation quality[1], the benefit of this strategy in different bowel preparation qualities was not reported. In this study, we report association between withdrawal time and polyp detection rate in various bowel preparation qualities during screening colonoscopy in an inner city Bronx, NY, United States hospital with a high rate of inadequate bowel preparation quality.

MATERIALS AND METHODS

Study setting and patients

This study was conducted at the Bronx Lebanon Hospital Center (Bronx, NY, United States) and approved by the hospital's institutional review board. All procedures were performed or directly supervised by six full-time and two part-time gastroenterologists. We reviewed the medical records of all patients who underwent screening colonoscopies between January 1, 2005 and June 30, 2011. Data was collected through ProVationMD, an onsite computer generated medical record system used by endoscopists to create patient reports immediately after procedures. The electronic records of all these patients were reviewed for age, sex, race, date, time of colonoscopy, indication of colonoscopy, family history of colon cancer, timing of colonoscopy, bowel preparation quality, duration of colonoscope withdrawal, and polyp findings. We also collected the names of endoscopists of each case along with their average adenoma detection rates in the last 3 mo.

As per institutional practice at the time, all patients who were evaluated for screening colonoscopy were given verbal and written instructions about diet and laxative use on the day before the procedure. All these patients were instructed to consume a clear liquid diet the day before the procedure, followed by 1 gallon of polyethylene glycol (PEG) solution starting at 6 PM the evening before the procedure. In addition, 20-25 mg of bisacodyl was taken at 9 PM. Several endoscopists started giving split doses of PEG in mid-2009 for patients who underwent screening colonoscopy in the afternoon. Patients undergoing procedures before noon were not expected to take laxatives on the day of the procedure. All colonoscopies which were performed before noon were categorized as morning procedures.

Table 1 Criteria used to classify bowel preparation quality

Bowel preparation quality	Criteria
Excellent	Mucosal detail clearly visible without washing (suctioning of liquid allowed
Good	Minimal turbid fluid in colonic segments and entire mucosa well seen after cleaning
Fair	There is minor residual material in the colonic segments. Necessary to suction liquid to adequately view the colonic segments
Poor	Necessary to wash and suction to obtain a reasonable view. Portion of mucosa in colonic segments seen after cleaning but up to 15% of the mucosa not seen because of retained material
Unsatisfactory	Solid stool not cleared with washing and suctioning. More than 15% of the mucosa not seen

Based on the ProVationMD reporting system, the bowel preparation quality was rated as unsatisfactory, poor, fair, good, or excellent. Criteria for each bowel preparation quality are shown in Table 1. All patients who were included in the study had an average risk of colorectal cancer. Screening colonoscopies were performed in an outpatient setting. Patients were excluded if the indication for colonoscopy was associated with an increased risk for colorectal cancer, which included constipation, anemia, weight loss, hematemesis, hematochezia, and positive fecal occult blood test. Other exclusion criteria included patients with a personal history of adenomatous polyps or colon cancer, prior colonic resection, significant family history of colorectal cancer, screening colonoscopy after other abnormal screening tests such as flexible sigmoidoscopy or barium enema, and screening colonoscopies during in-patient care.

Variables measured

We evaluated polyp detection outcome based on the distribution and total number of colonic polyps. Distribution of the colonic polyp was defined as the number of colonic segments found to have polyps. We divided the examined intestinal portion examined during colonoscopy into eight segments: (1) rectum; (2) sigmoid colon; (3) descending colon; (4) splenic flexure; (5) transverse colon; (6) hepatic flexure; (7) ascending colon; and (8) cecum. If a polyp or several polyps were found in a colonic

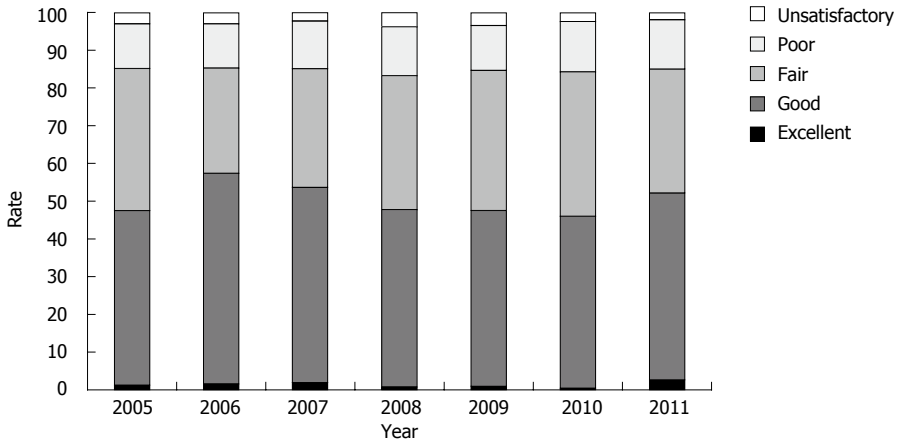

Figure 1 Distribution of bowel preparation quality for screening colonoscopies from January 1, 2005 to June 30, 2011.

segment, the colonic segment would be marked as containing polyps. Therefore, the maximum total number of colonic segments with polyps would be eight. We did not use adenoma detection rate as one of the measured outcomes, as we considered adenoma a pathologic diagnosis, not an endoscopic finding.

Statistical analysis

The data were collected and analyzed using IBM SPSS Statistics for MAC version 20. Colonoscopies without bowel preparation quality data were not included in further analysis. Bowel preparation quality was graded by the endoscopists as (1) excellent; (2) good; (3) fair; (4) poor; and (5) unsatisfactory or very poor. The five groups of bowel preparation quality were coded and classified as ordinal data. These groups were used as independent variables in the analysis. The mean duration of colonoscope withdrawal between each group of bowel preparation quality were compared by one-way ANOVA. We evaluated the differences in the number of intestinal segments with polyps and total number of colonic polyps between the five bowel preparation quality groups by Kruskal Wallis test.

Further analysis was performed to measure the correlation between polyp detection outcomes (number of colonic segments with polyps and total number of polyps) and withdrawal time using ordinal regression analysis. In this analysis, the number of intestinal segments with polyps or total number of colonic polyps was used as the dependent variable. Other variables, including withdrawal time and bowel preparation quality were included in this analysis as independent variables. Bowel preparation quality was an independent variable during subgroup analysis. Categorical data, such as race, sex, and the presence of a trainee during colonoscopy, were used as factors of independent variables. Continuous and ordinal data (*i.e.*, age, duration of colonoscope withdrawal, timing of colonoscopy, bowel preparation quality, adenoma detection rate of endoscopists, and duration of colonoscopy practice of endoscopists) were included as covariates of the independent variable. Odd ratios and 95%CI were calculated using exponents of estimates obtained from ordinal regression analysis. Statistical significance was defined as P-values ≤ 0.05.

RESULTS

During the study period, there were 8581 screening colonoscopies which fulfilled inclusion and exclusion criteria. There were 250 colonoscopies without documented information of bowel preparation quality, therefore a total of 8331 colonoscopies were used for further analysis. Of these 8331 colonoscopies, bowel preparation quality was distributed as follows: 1% was excellent, 49% were good, 35% were fair, 13% were poor, and 3% were unsatisfactory. The frequencies of bowel preparation quality for each year are shown in Figure 1. The mean age was 58.9 years (range 45-85 years), 58% were women, 24% were non-Hispanic Blacks, and 62% were Hispanic. Characteristics of the subjects based on the quality of bowel preparation are shown in Table 2.

Distribution of mean duration of colonoscope withdrawal based on bowel preparation quality is shown in Table 3. The longest mean duration of colonoscope withdrawal was seen among subjects with fair quality. Subjects with excellent bowel preparation quality had the shortest mean duration of colonoscope withdrawal.

The distribution of the number of colonic segments with polyps and total number of colonic polyps based on bowel preparation quality is shown in Table 3. The overall rate of subjects with no colonic polyps was 66% (5475/8331). The rate of patients with polyps in multiple colonic segments were 7% in the excellent group, 14% in good group, 18% in fair group, 12% in poor group, and 8% in unsatisfactory group.

Odd ratios for each variable in predicting a higher number of colonic segments with polyps and total number of polyps are shown in Table 4. Older age, male sex, longer duration of withdrawal time, bowel preparation quality and higher adenoma detection rate of endoscopist predicted a higher number of colonic segments with polyps and a higher number of polyps found during

Table 2 Patient characteristics based on bowel preparation quality *n* (%)

Characteristics	Quality of bowel preparation				
	Excellent (*n* = 108)	Good (*n* = 4051)	Fair (*n* = 2889)	Poor (*n* = 1045)	Unsatisfactory (*n* = 238)
Mean age ± SD, yr	58 ± 7.6	59 ± 7.6	59 ± 7.9	60 ± 7.7	59 ± 8.3
Women	65 (60)	2481 (61)	1596 (55)	537 (51)	117 (49)
Race					
Asian	1 (1)	32 (1)	16 (1)	4 (0)	0 (0)
White	1 (1)	47 (1)	34 (1)	15 (1)	5 (2)
Black	25 (23)	875 (22)	697 (24)	280 (27)	82 (35)
Hispanic	81 (75)	3097 (77)	2142 (74)	746 (71)	151 (63)
Morning procedure	45 (42)	1877 (46)	1212 (42)	428 (41)	78 (33)

Table 3 Withdrawal time and polyp detection based on bowel preparation quality *n* (%)

	Quality of bowel preparation					*P*-value
	Excellent (*n* = 108)	Good (*n* = 4051)	Fair (*n* = 2889)	Poor (*n* = 1045)	Unsatisfactory (*n* = 238)	
Mean duration of colonoscope withdrawal ± SD, min	10 ± 5.5	12 ± 5.3	13 ± 5.9	12 ± 5.2	11 ± 9.4	< 0.001
No. of colonic segments with polyps						< 0.001
0	85 (77)	2707 (67)	1799 (62)	703 (67)	181 (76)	
1	17 (16)	769 (19)	581 (20)	223 (21)	38 (16)	
2	3 (3)	375 (9)	305 (11)	74 (7)	13 (6)	
3	1 (1)	136 (3)	145 (5)	31 (3)	6 (3)	
4	2 (2)	43 (1)	38 (1)	11 (1)	0 (0)	
5	0 (0)	16 (0)	18 (1)	3 (0)	0 (0)	
6	0 (0)	2 (0)	3 (0)	0 (0)	0 (0)	
7	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	
8	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	
Total No. of colonic polyps						< 0.001
0	85 (77)	2707 (67)	1799 (62)	703 (67)	181 (76)	
1	13 (12)	581 (14)	446 (15)	42 (4)	30 (13)	
2	2 (2)	231 (6)	164 (6)	60 (6)	8 (3)	
3	4 (4)	256 (6)	195 (7)	37 (4)	10 (4)	
4	2 (2)	152 (4)	155 (5)	22 (2)	5 (2)	
5	1 (1)	73 (2)	90 (3)	6 (1)	4 (2)	
> 5	1 (1)	51 (1)	30 (1)	2 (0)	0 (0)	

colonoscopy. Non-Hispanic Black was a predictor for a higher number of polyps found during colonoscopy. However, the duration of colonoscopy practice of the endoscopist had an inverse relationship with the number of colonic segments with polyps and number of polyps found during colonoscopy. The mean ± SD adenoma detection rate of the endoscopist was 26% ± 8.3%. Of the colonoscopy procedures performed, 76.2% (6348/8331) of them performed by endoscopists with high adenoma detection rate, which was defined as a rate greater than 20%. In subgroup analysis, longer withdrawal time was associated with better polyp detection outcomes in patients with good, fair, or poor bowel preparation quality (Table 5). However, among those with excellent or very poor bowel preparation quality, longer duration of withdrawal time was not related to higher number of colonic segments with polyps and higher total number of colonic polyps.

DISCUSSION

Results of this study showed that half of screening colonoscopies in our minority-predominant community were performed with fair, poor, or unsatisfactory bowel preparation quality. The distribution of quality remained unchanged over the years, even though some providers started prescribing split-dose laxatives since mid-2009 for many patients undergoing afternoon screening colonoscopies. Therefore, modification of other factors, including longer withdrawal time, may improve polyp detection rate in this population.

Our study showed that the rate of colonoscopies with single colonic polyps and polyps in multiple colonic segments were highest among those with fair bowel preparation quality. In addition, this group of patients had the longest duration of colonoscope withdrawal. This likely includes patients who at presentation had poor or unsatisfactory bowel preparation quality but were cleaned in order to visualize the colon. This cleaning of intraluminal contents by diluting and suctioning has been recommended by the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology[4,12]. The rating of bowel preparation quality is to be given only after colon cleansing has taken place[12,13]. As a result of this cleansing process, the withdrawal time was prolonged.

Table 4 Predictors of higher number of colonic segments with polyps and total number of colonic polyps during screening colonoscopy

	No. colonic segment with polyps		Total No. colonic polyps	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Older age	1.01 (1.00-1.03)	0.011	1.01 (1.00-1.02)	0.026
Gender of male[1]	1.31 (1.11-1.55)	0.002	1.18 (1.00-1.39)	0.047
Race				
Asian[2]	0.89 (0.34-2.25)	NS	1.06 (0.41-2.73)	NS
White[2]	0.69 (0.33-1.45)	NS	0.70 (0.33-1.45)	NS
Black[2]	1.17 (0.97-1.41)	NS	1.22 (1.01-1.47)	0.041
Later time of colonoscopy	1.00 (1.00-1.00)	NS	1.00 (1.00-1.00)	0.043
Better bowel preparation quality	1.10 (1.00-1.21)	0.04	1.11 (1.01-1.22)	0.030
Longer duration of colonoscope withdrawal	1.14 (1.12-1.16)	< 0.0001	1.14 (1.12-1.16)	< 0.0001
Adenoma detection rate of endoscopist	1.03 (1.02-1.04)	< 0.0001	1.03 (1.02-1.04)	< 0.0001
Duration of colonoscopy practice of endoscopist	0.98 (0.97-0.98)	< 0.0001	0.98(0.97-0.99)	< 0.0001
Involvement of trainee during colonoscopy	0.93 (0.72-1.19)	NS	0.93(0.73-1.19)	NS

[1]Compared to gender of female; [2]Compared to Hispanic. NS: Not statistically significant.

Table 5 Association between longer withdrawal time and higher polyp detection in various bowel preparation qualities

	No. of colonic segments with polyps		Total No. colonic polyps	
	OR (95%CI)[1]	*P*-value	OR (95%CI)[1]	*P*-value
Excellent	1.07 (0.99-1.26)	NS	1.11 (0.99-1.24)	NS
Good	1.16 (1.13-1.19)	< 0.0001	1.15 (1.13-1.18)	< 0.0001
Fair	1.13 (1.10-1.17)	< 0.0001	1.13 (1.10-1.16)	< 0.0001
Poor	1.18 (1.11-1.26)	< 0.0001	1.20 (1.13-1.29)	< 0.0001
Unsatisfactory/very poor	1.02 (0.99-1.12)	NS	1.05 (0.99-1.10)	NS

[1]Adjusted to age, gender, race, timing of colonoscopy, endoscopist adenoma detection rate, duration of colonoscopy practice of endoscopists, involvement of trainee during colonoscopy. NS: Not statistically significant.

Multivariate analysis of our data showed that older age, male sex, longer duration of colonoscope withdrawal, bowel preparation quality, and higher endoscopist adenoma detection rate were independent predictors of higher number of colonic segments with polyps and a higher number of total polyps. Older age, male sex, and adenoma detection rate of the endoscopist were previously reported to be associated with higher polyp detection[14-17], but these factors are not modifiable during a colonoscopy procedure. On the other hand, longer duration of colonoscope withdrawal is an operator-dependent factor, which may be used as a compensatory measure when encountering inadequate bowel preparation quality. In addition, many studies have confirmed the association between this modifiable factor and adenoma detection[1,17-19].

Analysis of each bowel preparation quality group showed that longer withdrawal time was not associated with higher number of colonic segments with polyps or higher total number of colonic segments in those with excellent or unsatisfactory bowel preparation quality. These data may explain the findings of studies reporting no relationship between longer withdrawal time and polyp or adenoma detection rate. Sawhney *et al*[10] reported that the establishment of a mandatory withdrawal time of $\geqslant$ 7 min produced a significant increase in the compliance rate for withdrawal time from 65% to 100%. However, in spite of this, there was no concomitant increase in polyp detection ratio noted for all polyps (slope 0.0006; $P = 0.45$) or for 1-5 mm (slope 0.001; $P = 0.26$), 6-9 mm (slope 0.002; $P = 0.43$), or $\geqslant$ 10 mm polyps (slope 0.006; $P = 0.13$)[10]. A study by Moritz *et al*[11] also reported that withdrawal time was not associated with detection of polyps > 5 mm in size in a prospective cohort study. In addition, recording of withdrawal time or implementing a withdrawal time policy of > 7 min was not associated with a significant increase in colonic polyp detection[20]. However, all the aforementioned studies did not analyze the effect of withdrawal time based on bowel preparation qualities. It is worth pointing out that with an excellent bowel preparation quality, the completeness of evaluation might have been at a maximum that could not be improved with prolonged withdrawal time. On the other hand, prolonged withdrawal time for cleansing and evaluating the colonic mucosa of those with unsatisfactory or very poor bowel preparation is unlikely to remove solid or semi-solid stool. Therefore, aborting the procedure may be a reasonable option.

Our data showed that a longer duration of colonoscopy practice of endoscopist was inversely associated with a higher polyp detection rate. Harris *et al*[21] reported that colonoscopies in centers where over 50% of the endoscopists were of senior rank had a higher adenoma detection rate than centers with fewer senior endoscopists.

However, the senior endoscopists may have had more patients with a high risk of developing colonic polyps. In addition, the study included diagnostic procedures and colonoscopies for patients with increased risk of colonic cancer. Our finding indicates that the colonoscopy technique (*i.e.*, longer duration of colonoscope withdrawal) and better bowel preparation quality are important factors for senior endoscopists to achieve a higher polyp detection rate during screening colonoscopy in individuals with an average risk.

There are several limitations of this study, including its retrospective nature. In this study, we used overall bowel cleanliness, rather than segmental cleanliness of the bowel. The bowel preparation quality was not assessed for the right colon (cecum, ascending), mid-colon (transverse, descending), and recto-sigmoid, individually. Nonetheless, recent retrospective studies[22-25] of bowel preparation quality included the total bowel preparation scale score for the assessment. Of note, this study defined polyp detection as the number of colonic segments with polyps and number of polyps rather than adenoma detection rate of each colonoscopy. We believe that this outcome measurement reflects the overall colon condition and its endoscopic, not pathologic, lesions. Moreover, a recent study showed that the difference between benign, pre-malignant, and malignant colorectal polyps could not be accurately predicted visually alone[26]. Therefore, all polyps visualized during colonoscopy need to be excised for *ex vivo* histology regardless of size, location, or predicted pathology.

In summary, based on these data, the longest duration of colonoscope withdrawal time and highest colonic detection rate occurred in colonoscopies with fair quality. Similar to previous studies[1,10,27,28], we found that colonic segments with polyps and total number of colonic polyps are affected by colonoscopic withdrawal time. Further analysis showed that longer withdrawal time was not associated with higher polyp detection among those with an extreme spectrum of bowel preparation quality (*i.e.*, excellent and unsatisfactory/very poor). This study finds that prolonged withdrawal time in those with good, fair, and poor bowel preparation quality is likely beneficial to improving polyp detection during screening colonoscopy.

COMMENTS

Background

Many factors influence the finding of colonic polyps during colonoscopy, including clear visualization of the colonic mucosa and completeness of the examination. The presence of a significant amount of stool requiring washing and suctioning prolongs the duration of the colonoscope withdrawal. In contrast, the withdrawal time could be faster in patients with high-quality bowel preparation. The benefit of prolonged duration of colonoscope withdrawal in various degrees of bowel cleanness has not been evaluated.

Research frontiers

One study with a large number of samples found that prolonged colonoscope withdrawal time was associated with higher polyp detection rates and that the overall median polyp detection corresponded to a withdrawal time of > 6.7 min. Based on this study, United States gastroenterology societies recommend that the average colonoscope withdrawal time should exceed 6 min, not including time spent for removal of the polyps. However, since the implementation of this recommendation, quality improvement efforts, such as by simply mandating a minimal withdrawal time, have largely proven to be unsuccessful in significantly improving the polyp detection rate.

Innovations and breakthroughs

In this article, the authors showed that half of the screening colonoscopies in minority-predominant community were performed with inadequate bowel preparation quality. Moreover, the rate remained unchanged over the years, even though some providers started new methods of preparation. The authors then showed that prolonged colonoscope withdrawal by endoscopists practicing in this community was beneficial for the majority of cases, except for those with very poor and excellent bowel preparation qualities.

Applications

The findings of this study suggest aborting screening colonoscopy procedure in those with very poor bowel preparation quality because a prolonged duration of the colonoscope procedure is unlikely beneficial. On the other hand, prolonging colonoscope withdrawal time by more than the recommended duration in patients with an excellent quality of bowel preparation increases sedation time without benefits in polyp detection.

Terminology

A colonoscopy is an endoscopic procedure to detect and remove polyps in the large bowel (colon). Polyps in the colon have potential to become cancer. Detail evaluation of the colon is performed while withdrawing the colonoscope after reaching the beginning segment of the colon. Bowel preparation quality is considered unsatisfactory or very poor if the colon contains solid stool that does not clear with washing and suctioning. In this situation, more than 15% of the large bowel wall is not seen. If the detail of the colonic wall is clearly visible without washing, then the bowel preparation quality is considered to be excellent.

Peer review

It provides new information, particularly for young gastroenterologists and other doctors regarding polyp screening policies. It is a very interesting article and is well documented.

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CLINICAL TRIALS STUDY

Using motion capture to assess colonoscopy experience level

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Abstract

AIM: To study technical skills of colonoscopists using a Microsoft Kinect™ for motion analysis to develop a tool to guide colonoscopy education.

RESULTS: Ten experienced endoscopists (gastroenterologists, *n* = 2; colorectal surgeons, *n* = 8) and 11 novices participated in the study. A Microsoft Kinect ™ recorded the movements of the participants during the insertion of the colonoscope. We used a modified script from Microsoft to record skeletal data. Data were saved and later transferred to MatLab for analysis and the calculation of statistics. The test was performed on a physical model, specifically the "Kagaku Colonoscope Training Model" (Kyoto Kagaku Co. Ltd, Kyoto, Japan). After the introduction to the scope and colonoscopy model, the test was performed. Seven metrics were analyzed to find discriminative motion patterns between the novice and experienced endoscopists: hand distance from gurney, number of times the right hand was used to control the small wheel of the colonoscope, angulation of elbows, position of hands in relation to body posture, angulation of body posture in relation to the anus, mean distance between the hands and percentage of time the hands were approximated to each other.

RESULTS: Four of the seven metrics showed discriminatory ability: mean distance between hands [45 cm for experienced endoscopists (SD 2) *vs* 37 cm for novice endoscopists (SD 6)], percentage of time in which the two hands were within 25 cm of each other [5% for experienced endoscopists (SD 4) *vs* 12% for novice endoscopists (SD 9)], the level of the right hand below the sighting line (z-axis) (25 cm for experienced endoscopists *vs* 36 cm for novice endoscopists, $P < 0.05$) and the level of the left hand below the z-axis (6 cm for experienced endoscopists *vs* 15 cm for novice endoscopists, $P < 0.05$). By plotting the distributions of the percentages for each group, we determined the best discriminatory value between the groups. A pass score was set at the intersection of the distributions, and the consequences of the standard were explored for each test. By using the contrasting group method, we showed a discriminatory value of Z = 1.51 to be the pass/fail value of the data showing discriminatory ability. The pass score allowed all ten experienced endoscopists as well as five novice endoscopists to pass the test.

CONCLUSION: Identified metrics can be used to discriminate between experienced and novice endoscopists and to provide non-biased feedback. Whether it is possible to use this tool to train novices in a clinical setting requires further study.

Key words: Colonoscopy; Assessment; Simulation; Motion-capture; Motion-analysis

Core tip: Motion capture for motion analysis can be

used to discriminate between experienced and novice performers of colonoscopy. We analyzed the motion patterns of the technical procedure of inserting the colonoscope from anus to cecum in a simulation set-up. The technical differences between novice and experienced endoscopists observed in this study are important because they can help shape skills that will lead to competence in colonoscopy. In the future, this technique might be useful in the training and education of future colonoscopists in a clinical setting.

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INTRODUCTION

Screening programs for colorectal cancer and concern for patient safety have increased the importance of training endoscopists for competency in colonoscopy. The workload of existing endoscopy units is often high, with units performing an increasing number of endoscopies in addition to supervising, training and instructing future endoscopists. The quality of colonoscopies was questioned in an investigation of 68 endoscopy units in the United Kingdom with a cecal intubation rate of 56%. Only 17% of the endoscopists had supervised training during their introduction to colonoscopy, and only 33% attended a colonoscopy course[1]. In Denmark, colonoscopy competence is solely based upon educational level, such as having a specialized degree in gastroenterology and/or surgery. The number of colonoscopies performed has conventionally defined technical competence in colonoscopy, and a threshold number of up to 275-500 has been suggested[2,3]. Previous methods for assessing skills in colonoscopy have been based upon subjective expert ratings, and previous tools have been based upon the procedural endpoints, time to cecum, depth of insertion or complication rate of therapeutic procedures[4-6]. No automatic assessment tools have been developed, although it has been noted that an optimal assessment tool in surgical skills should be based upon objective and structured criteria[7]. However, some progress has been made with regards to a benchmarked curriculum for virtual reality colonoscopy simulators[8].

Colonoscopy is very much dependent upon manual dexterity, correct stance and hand-eye coordination. The correct way to perform a colonoscopy is greatly debated, and some variations have been noted among experts advocating for the single-handed technique[9-13]. Video imaging has been found to be valuable in assessing competence in surgical skills[7], and video-based judgment of the handling of endoscopes is one of the main basic colonoscopy procedures tested with the "Direct Observation of Procedural Skills Score (DOPS)"[14].

It is a well-known but unproven fact among professional gastroenterologists that the stance of the performer shows the level of competence. Defining a "correct" basic handling in colonoscopy is not easy, but certain facts are clear: when adhering to the single-handed technique[9,10,13], the procedure should be conducted in a relaxed fashion with a straight scope, with minimal discomfort for the endoscopist as well as for the patient. Concerning movements of the tip of the scope, torque steering and steering with the small wheel of the colonoscope has very little effect when the tip is angulated[15].

The correct single-handed technique has been tested by video imaging with an objective structured video assessment tool where instrument grip, tip steering, and letting go of the instrumental shaft all were found to correlate with the competence level of the endoscopist[9]. The same basic colonoscopy metrics were found to improve significantly in an intensive training program[10].

Motion analysis has been used to teach correct skiing technique in downhill skiing to prevent injuries[16] and to correct golf swings[17]. Motion analysis can also be used to determine joint movements in different procedures, such as walking in high-heeled shoes to explain the occurrence of gait related diseases[18]. We speculate that motion analysis could also be used to teach correct movements in colonoscopy performance, if correct movements can be identified and verified.

In medicine, motion analysis has been used to identify skilled performers in emergent endotracheal intubation in physical models[19] as well as in an infant airway trainer[20]. Previously, motion analysis demanded the use of sensors on the body, making analysis of movements a costly process. In 2012, Microsoft launched the Microsoft Kinect (MS Kinect) system for Windows, designed for the XBOX gaming platform. The MS Kinect camera has become increasingly popular in many areas aside from entertainment. It provides a quick, cheap and easy way of analyzing position and mapping 3-dimensional (3D) pose data, providing skeletal movement tracking. The accuracy of the system as a peripheral device measuring 3D depth is estimated to be 1-4 cm at a range of 1-4 m[21].

The aim of this study was to use the MS Kinect system to automatically record and analyze the components of the basic techniques of endoscopists (experienced endoscopists and novices), selecting discriminatory metrics to develop a tool which can monitor competence in endoscopists and guide education in a non-biased way.

MATERIALS AND METHODS

Participants

Ten consultants experienced in endoscopy (gastroenterologists, n = 2; colorectal surgeons, n = 8) and eleven novices participated in the study. Novices were recruited from fellows in gastroenterology and gastroenterological surgery during their first or second year of fellowship and had very limited experience in colonoscopy (median 0 procedures, range 0-2). The experienced group had an average of 18.3 years of endoscopic experience

Table 1 Demographic details on the participation physicians

	Sex		Age, yr		Colonoscopy experience		Colonoscopies performed in past 12 mo	
	Male	Female	Median	Range	Median	Range	Median	Range
Novices (n = 11)	4	7	32	(28-37)	0	(0-2)	0	(0-2)
Experienced endoscopists (n = 10)	8	2	55	(42-63)	2000	(350-4000)	52.5	(0-450)

(range 7-30) and had performed a median of 2000 (range 350-4000) colonoscopies, including a median of 75 (range 0-450) colonoscopies within the last year (Table 1). All participants were recruited and tested between November 2012 and March 2013.

Study set-up

We used a virtual reality simulator for the introduction to the functions of the colonoscope (GI Mentor, Simbionix Corporation, United States). For the test, we used the Kagaku Colonoscope Training Model (Kyoto Kagaku Co. Ltd, Kyoto, Japan) and a colonoscope (Olympus™ CF 180AL) with air insufflation, suction-water knobs and a scope guide from Olympus. The physical model consisted of a flexible rubber "colon" tube inside of a life-size mannequin. The colon tube could be adjusted into 6 different positions using Velcro-strips and rubber bands. Tasks 1 (test introduction) and 3 (test) were chosen for this study. Task 1 was a technically easy procedure, whereas task 3 was more challenging, with a loop formation in the sigmoid colon. The test setting was a fixed set up in a dedicated room and was not changed during the study period.

Data collection

Testing was conducted in a medical simulation center. The novices were introduced to the functions of the colonoscope including handling the colonoscope, using the controls (*i.e.*, dials, insufflation, suction, and water), manipulating the endoscope tip, and torque steering in a virtual-reality simulator. The training session was 1 hour. All participants were asked to fill out a brief questionnaire, which included demographics, such as gender, age, years of endoscopic experience and the number of colonoscopies performed during the past 12 mo. A letter of acceptance of participation was handed out, signed and returned prior to the test. Participants were instructed to treat the model as if it were a real patient. The participants were informed that their movements would be recorded but were given no details of which metrics would be measured. They were given a maximum of 15 min to perform the procedure. A Kinect camera recorded the movements of the participant during insertion of the scope. Recording was initiated at intubation of the rectum and stopped when the scope reached the cecum.

Microsoft Kinect

The Kinect camera consists of a series of external sensors for image capturing and is motorized to make the box adjustable. The sensors are able to detect movements without requiring the participants to wear tracking sensors.

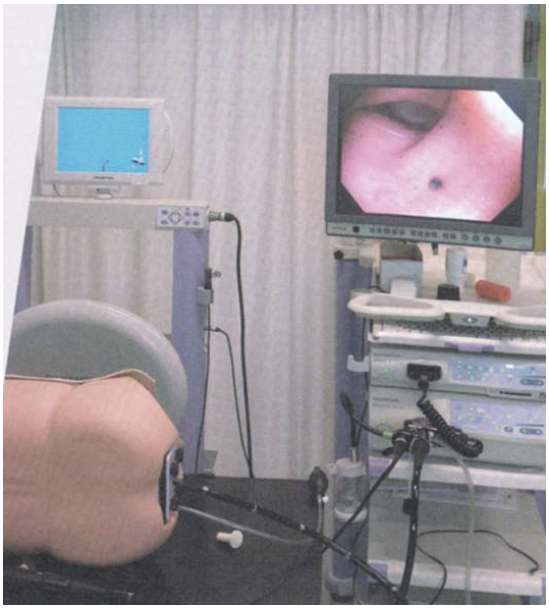

Figure 1 The simulator set-up. The Kinect was placed behind the two screens.

The Kinect creates a map of reflections from the person in the scene, which can be used for skeleton analysis. We used a modified script from Microsoft for recording skeletal XYZ-data. Data were saved and later transferred to MatLab® 2012a for analysis and the calculation of statistics. The range of the Kinect system for depth analysis is 1.2-3.5 m; the test set-up was adjusted to this distance. The box was placed above the endoscopy screen pointing at the chest of the participants, producing an image of the upper part of the body (Figure 1). The setup was not adjusted according to the height of the participants but all participants were within the range of the camera. The coordinates of the Kinect system are shown in Figure 2. The Z-axis was pointed at the chest, and the X-axis was longitudinal to the gurney.

Measured metrics

Validated tools, such as DOPS, suggest metrics related to basic techniques, such as the correct use of the left and right hands and understanding looping and cecal intubation[10]. However, there is no defined correct way of handling the scope during insertion. We chose a number of measures, skeletal angles and joint movements we thought appropriate to the procedures based on the literature[15].

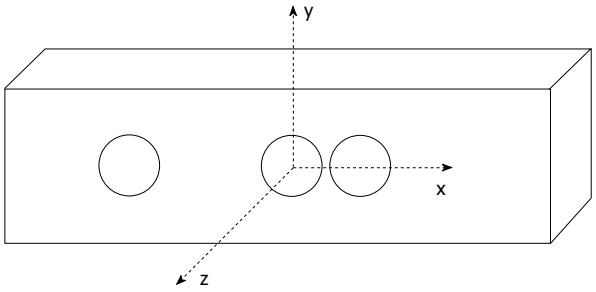

Figure 2 3D coordinates of the Kinect system.

Metrics used for motion analysis were the distance of the right and left hands from the gurney, the number of times the right hand was used to control the small wheel (distance between hands less than 25 cm), the angulation of the right and left elbows, the position of the hands in relation to the torso, the angulation of body posture in relation to the orifice, the mean distance of the hands from each other during the procedure and the percentage of time the hands were approximated. Measurements were conducted at 30 frames per second, and for each person, a mean of values was calculated in relation to coordinates of the MS Kinect.

Statistical analysis

All variables showing statistically significant differences between novices and experienced operators were identified using independent sample *t*-tests. The means and standard deviations of the experienced group were used to transform variables with discriminative ability into Z-scores. These Z-scores, when discriminatory, were intended to be averaged into a single score for each participant; *i.e.*, a score of 2 indicated that the participant, on average, was two standard deviations off the "gold standard", defined by the mean of experienced operators. A pass-fail standard was set using the contrasting groups method to further explore the ability of this aggregated score to discriminate between the two groups.

An independent samples *t*-test, Mann-Whitney test and Levene's test for equality of variance were performed to compare the performances of the two groups. Spearman's rho was used for non-parametric correlation analysis.

Statistical analysis was performed using a statistical software package (r-project.org, R v 3.0.2; MatLab® 2012a). Differences were considered to be statistically significant for P values < 0.05.

RESULTS

The two groups differed in gender (experienced endoscopists: 2 females, 8 males; novices: 7 females, and 4 males) (NS, Fisher's test) and age. For details see Table 1.

Only four of our seven metrics showed discriminatory ability between novice endoscopists and experienced endoscopists in the *t*-test (test of mean), and only two showed a difference in group-variance.

Table 2 Metrics analysed for discriminatory ability

Kinect metrics	Experienced endoscopist	Novice	Levene's test	*P* value
Percentage of time with hands closer than 25 cm (%)	7	23	0.048	0.02
Distance between hands (cm)	45	37	0.09	0.01
Angle of shoulders (degrees)	17	20	0.95	0.38
Right hand below z-line (cm)	25	36	0.95	0.01
Mean distance shoulder-hand (cm)	31	31		
Left hand above z-line (cm)	6	15	0.03	0.005
Mean distance: shoulder-hand (cm)	32	31		
Left elbow (degrees)	91	92	0.86	0.81
Right elbow (degrees)	144	140	0.55	0.55
Height participants (cm)	39	30	0.08	0.02
Compared to coordinates				

Three metrics: "angulation of right elbow," "angulation of left elbow" and "angulation of shoulders to the anus of physical model" did not show discriminatory ability.

We found discriminatory values for the following metrics: "level of left hand" and "level of right hand" below the z-axis (experienced: 6 cm for the left hand; novices: 15 cm for the left hand, $P < 0.05$; experienced: 25 cm for the right hand; novices: 36 cm for the right hand, $P < 0.05$). The difference subsided when correcting for the height of the person by analyzing the distance of the left and right hands from the left and right shoulders accordingly (31 cm *vs* 32 cm, NS). The two groups differed in height when shoulder height was analyzed. For details see Table 2.

Two metrics showed discriminatory ability: "mean distance between hands" [experienced: 45 cm (SD 2); novices: 37 cm (SD 6)] and "percentage of time with hands less than 25 cm apart" [experienced: 5% (SD 4); novices: 12% (SD 9)].

Absolute Z-scores (average standard deviations from the "gold standard") were calculated for each of the discriminatory metrics and summed to a total mean Z-score for each participant. For details, see Table 3.

By plotting the distributions for each group, we could determine the best discriminatory value between the groups. The pass score was set at the intersection of the distributions, and the consequence of the standard was explored for each test. By using this contrasting group method, we showed a discriminatory value of Z = 1.51 to be the pass score. The pass score allowed all of the experienced as well as the five novices to pass the test (Figure 3).

Nine of ten of the experienced operators reached the cecum within 15 min (the cut-off time), as did seven out of 11 novices (64%). Comparing Z-scores, pass *vs* cecal intubation ability's positive PV for a passing Z-score was found to be 80%, while the negative PV for cecal intubation for a failed Z-score was 33%.

Table 3 Experience correlated to pass score and cecal intubation rate

Test person	Competence	Total colonoscopies	Colonoscopies in last year	Z mean	Z-score passed	Cecal intubation
1	Experienced Endoscopist	3000	300	1.15	Yes	Yes
2	Experienced endoscopist	400	10	1.32	Yes	Yes
3	Experienced endoscopist	2000	0	1.25	Yes	Yes
4	Experienced endoscopist	1000	17	0.08	Yes	Yes
5	Experienced endoscopist	1700	150	0.30	Yes	Yes
6	Experienced endoscopist	4000	232	0.70	Yes	Yes
7	Experienced endoscopist	3000	14	0.78	Yes	Yes
8	Experienced endoscopist	2000	450	0.76	Yes	Yes
9	Experienced endoscopist	2000	75	0.82	Yes	Yes
10	Experienced endoscopist	350	30	0.73	Yes	Yes
11	Novice	0	0	1.54	No	No
12	Novice	0	0	1.48	Yes	No
13	Novice	0	0	1.28	Yes	Yes
14	Novice	0	0	2.26	No	Yes
15	Novice	1	1	6.19	No	Yes
16	Novice	0	0	0.27	Yes	Yes
17	Novice	0	0	6.50	No	No
18	Novice	0	0	5.25	No	Yes
19	Novice	0	0	1.17	Yes	No
20	Novice	0	0	3.25	No	Yes
21	Novice	2	2	0.65	Yes	No

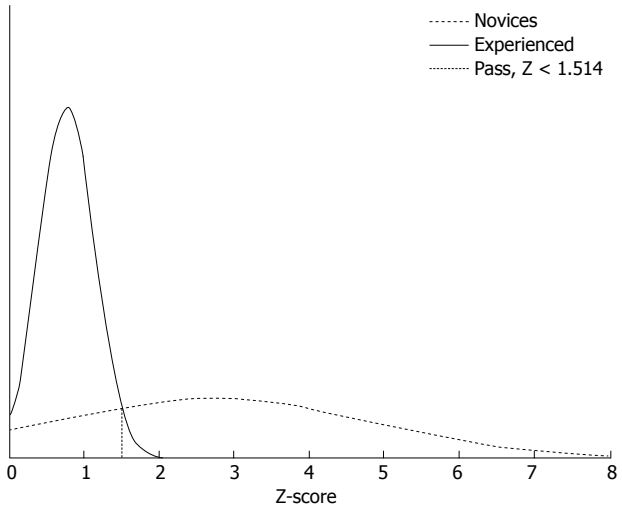

Figure 3 Establishing a pass/fail standard using the contrasting-groups method. The distribution of scores of novices (dotted line) and experienced (solid line). The pass score (Z-1,51) is set at the intersection of the score distributions of the two groups.

There was no difference in the novices who reached the cecum and the novices who did not reach the cecum in regards to percentage of time when the hands were less than 25 cm apart (14%). When measuring the distance between hands, there were no group differences among the novices (37 cm).

Time to reach the cecum was measured. A positive correlation Rho was found for "percentage of time with hands too close," "hand distance" and "cecal intubation time" (Rho = -0.58; $P = 0.005$ and Rho = 0.60; $P = 0.004$).

There was no correlation between the aggregated Z-score and time to cecum (Rho = 0.40; NS). However, when analyzing the correlation between the numbers of colonoscopies performed in the past year (Log routine) and the aggregated Z-score, a correlation was found (Rho = -0.54; $P = 0.01$).

DISCUSSION

Our data showed a difference in motion patterns of the colonoscopy procedure when comparing novices to experienced endoscopists. By using the MS Kinect, we could identify a common stance used by experienced endoscopists. Our data made it possible to note how the novices handled the colonoscope as they tried to control the tip. We found that excessive correction movements halted the progress of the colonoscope.

We found no correlation between the total score and time to cecum, which indicates that progression does not entirely depend on manual handling of the control dials of the colonoscope. We did, however, find a correlation between current routine (past years experience) and the Z-score, suggesting that other aspects of the steering process must be important. The reason for this might be the ability to keep the scope straight. Having a straight scope inside of the patient depends on a scope without loops and bends outside of the patient and a slack loop between hands. We found that the distance between hands was significantly wider in the experienced group, which might make "torque steering" easier[15]. The MS Kinect could not record the motion pattern of torque steering.

Assessment tools based on tri-split video monitoring and evaluation by trained judges have been made and validated by others[9,22]. DOPS assesses different domains of the colonoscopy procedure: basic handling of the colonoscope, such as "grip of instrument with accurate finger/thumb," "control of wheels," "tip steering" and "manipulation of the shaft".

The metric "distance between hands" was a surrogate measure of keeping the scope straight. We considered our data for "percentage of time with hands too close"

to be a surrogate measure of using both hands on the control dials (distance less than 25 cm). The DOPS metric "incorrect use of hand grip" was found to be one of the most significant metrics, showing improvement with a week of intensive training[10]. Using both hands on the steering wheel stopped the progression of the scope. We demonstrated an unbiased measure using "percentage of time with hands too close" to assess this parameter.

The ability to reach the control dials with the thumb can be challenging because the grip of the standard colonoscope has been developed for large hands. Endoscopists compensate by bringing the right hand up to help adjust the control dials. Cohen and colleges made an informative survey and found that 23% of fellow gastroenterologists felt that they had some difficulties in reaching and manipulating the horizontal control dial (small wheel). A considerable portion of the female fellows reported that their hands were too small to reach the horizontal control dial (40%), and nearly 80% reported that their hand size affected their ability to learn endoscopy[23]. The "left-hand grip"[12] and the "pinkie maneuver"[11] are methods to maneuver the control dials to compensate for this challenge. However, both methods result in a bended scope, which might negatively affect progression. Traditionally, ergonomic concerns have not played a large role in teaching the colonoscopy procedure. Tenosynovitis of the left thumb associated with overuse during endoscopy has been described (DeQuervain's syndrome), and this problem has increased with an increased number of procedures performed per endoscopist[24]. A solution to both problems could be the introduction of the scope-dock system developed for the ERCP procedure in colonoscopy. A docking system would allow for free handling of control dials simultaneous to torque steering and advancing the tip of the scope.

The aggregated score of our two significant metrics has demonstrated the ability to differentiate between experienced and novice endoscopists, and the pass score had a predictive value of 80% for reaching the cecum. Current routine in colonoscopy was highly correlated to the metrics with discriminatory ability. The combined Z-score, with a correlation coefficient of 0.54, made the Z-score an objective assessment tool to predict the ability to reach the cecum in a routine colonoscopy.

The advantage of the MS Kinect system is that it provides information on the motion pattern with an inexpensive and simple method[25]. The method has been found to be accurate in skeletal tracking of upper body movements as well as for joint measurements with an accuracy of 1-2 cm for a distance of up to 4 m[21].

Our assessment tool provides information that emphasizes that training should focus on handling the control dials, especially the small horizontal control dial, with the left hand and keeping a straight scope with a distance between the hands. Our data show that it was possible to recognize the motion pattern of experienced endoscopists by external motion capture and to distinguish the experienced from the novices in an objective way. We found a correlation between the current routine and the metrics with discriminatory ability, suggesting that correcting the stance might be relevant, not only in novices.

Whether it is possible to use this information from stance recognition and pose enforcement to train novices in a clinical setting remains to be determined, but this unbiased tool does provide useful information to guide teaching. Our tool might help colonoscopy trainees gain competence in the technical part of the colonoscopy procedure, which is the difficult and strenuous part of the procedure for the endoscopists, as well as for the patient.

COMMENTS

Background

Colonoscopy is a technically challenging procedure that requires the development of advanced psychomotor skills. During the past decade there has been increased focus on structured medical education and the assessment of procedural skills. Competence in colonoscopy has conventionally been defined as the number of colonoscopies performed or as rates of successful intubation of the cecum. Only a few attempts have been made to measure technical competence in colonoscopy. This study brings new objective information for learning technical skills of colonoscopy using motion capture.

Research frontiers

Motion analysis has been used in sports for decades. Using motion capture in colonoscopy provides new, useful, objective information to guide novices and those teaching colonoscopy so that competence in this procedure can be measured.

Innovations and breakthroughs

Previously, motion analysis required the use of sensors on the body, making the analysis of movements a costly process. In 2012, Microsoft launched the Microsoft Kinect (MS Kinect) system for Windows, designed for a gaming platform. The MS Kinect camera has become increasingly popular in many areas aside from entertainment and has been used in other areas of medical education.

Applications

Motion capture seems useful for obtaining objective measures to guide colonoscopy education and can be used in a clinical setting to provide unbiased feedback to guide novices and those teaching colonoscopy so that competence in this procedure measured by other gauges can be achieved.

Terminology

Motion capture: The process of recording the movement of people; Assessment tool: A method to assess performance; DOPS: Direct Observation of Procedural Skills Score is a validated assessment tool for the colonoscopy procedure.

Peer review

The authors address an important and relevant topic in today's teaching and learning of endoscopy and bring new objective information for learning its technical skills. The paper is very interesting.

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META-ANALYSIS

Early precut sphincterotomy and the risk of endoscopic retrograde cholangiopancreatography related complications: An updated meta-analysis

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Abstract

AIM: To study the cannulation and complication rates of early pre-cut sphincterotomy *vs* persistent attempts at cannulation by standard approach.

METHODS: Systematic search of PubMed, EMBASE, Web of Science, and the Cochrane Library for relevant studies published up to February 2013. The main outcome measurements were cannulation rates and post-endoscopic retrograde cholangiopancreatography (ERCP) complications. A comprehensive systematic search of the Cochrane library, PubMed, Google scholar, Scopus, National Institutes of Health, meta-register of controlled trials and published proceedings from major Gastroenterology journals and meetings until February 2013 was conducted using keywords. All Prospective randomized controlled trials (RCT) studies which met our inclusion criteria were included in the analysis. Prospective non-randomized studies and retrospective studies were excluded from our meta-analysis. The main outcomes of interest were post-ERCP pancreatitis, overall complication rates including cholangitis, ERCP-related bleeding, perforation and cannulation success rates.

RESULTS: Seven RCTs with a total of 1039 patients were included in the meta-analysis based on selection criteria. The overall cannulation rate was 90% in the pre-cut sphincterotomy *vs* 86.3% in the persistent attempts group (OR = 1.98; 95%CI: 0.70-5.65). The risk of post-ERCP pancreatitis (PEP) was not different between the two groups (3.9% in the pre-cut sphincterotomy *vs* 6.1% in the persistent attempts group, OR = 0.58, 95%CI: 0.32-1.05). Similarly, there was no statistically significant difference between the groups for overall complication rate including PEP, cholangitis, bleeding, and perforation (6.2% *vs* 6.9%, OR = 0.85, 95%CI: 0.51-1.41).

CONCLUSION: This meta-analysis suggests that pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates. Early pre-cut implementation does not increase PEP complications.

Key words: Post-cholangiopancreatography pancreatitis; Pre-cut sphincterotomy; Persistent attempts; Meta analysis

Core tip: Selective cannulation of the bile duct remains the limiting step in therapeutic post-endoscopic retrograde cholangiopancreatography (ERCP). Greater than 90% of cannulation is achieved through standard techniques. In 10% of patients, cannulation is difficult and requires additional techniques such as pre-cut

sphincterotomy. Early use of pre-cut sphincterotomy is suggested as a means to prevent excessive and repetitive papillary trauma which may in turn increase the risk of post-ERCP pancreatitis. The use of pre-cut sphincterotomy has been considered to increase risk of post-ERCP complications, in particular post-ERCP pancreatitis. We studied the literature on the use of pre-cut sphincterotomy in biliary access. Our meta-analysis showed that pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates including post-ERCP pancreatitis. Early pre-cut implementation does not increase PEP complications.

Navaneethan U, Konjeti R, Venkatesh PGK, Sanaka MR, Parsi MA. Early precut sphincterotomy and the risk of endoscopic retrograde cholangiopancreatography related complications: An updated meta-analysis. *World J Gastrointest Endosc* 2014; 6(5): 200-208 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i5/200.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i5.200

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been widely used for treatment of a variety of biliary disorders and cannulation of the bile duct remains one of the most important steps for successful therapeutic endoscopy. The success of biliary cannulation depends on several factors including patient anatomy, utilization of specialized catheters, and the skill and experience of the endoscopist[1]. Deep biliary cannulation by an experienced endoscopist using standard cannulation techniques is successful in approximately 90% of the cases[1]. Biliary cannulation becomes difficult in about 5%-10% of the cases[2,3] especially in patients with abnormal anatomy, ampullary or pancreatic tumors, and periampullary diverticuli. Precut sphincterotomy, also referred to as needle knife sphincterotomy (NKS), has been advocated in situations where routine biliary cannulation has been unsuccessful. The presumed risks and morbidity associated with NKS, particularly risk of post-ERCP pancreatitis (PEP) has discouraged use of this technique in patients with difficult biliary access[4]. The assessment of this risk, however, is confounded by pre-cut sphincterotomy being done as a last resort after repeated failed attempts at biliary cannulation and in some cases repeated inadvertent pancreatic duct (PD) cannulations. Repeated failed attempts at biliary cannulation and repeated pancreatic duct cannulations have been shown to be independently associated with a higher incidence of PEP[5-7]. In addition to PEP, reported complications of NKS are bleeding[8] and perforation[9]. The main goal of therapeutic ERCP is to achieve biliary cannulation with least possible adverse events. Early use of pre-cut sphincterotomy is suggested as a means to prevent excessive and repetitive papillary trauma which may in turn increase the risk of PEP. The few randomized controlled trials (RCTs) that have tried to assess the differences in the complication rates between early pre-cut sphincterotomy and persistent cannulation groups, have shown variable results and are limited by small number of patients and therefore inadequate power to demonstrate any potential differences between the groups[10-12].

An earlier meta-analysis demonstrated that early pre-cut sphincterotomy reduces PEP risk but not the overall complication rate or cannulation success[13]. Subsequent to this publication, another RCT has been published[14]. This study showed that early use of NKS during difficult cannulation does not increase the risk of PEP. Given the importance of this topic for the clinical practice of ERCP, we sought to perform an updated meta-analysis to study the differences in cannulation rates, PEP and overall complication risk between early pre-cut sphincterotomy and persistent attempts at cannulation, taking the new randomized study into consideration.

MATERIALS AND METHODS

Search strategy

Two authors (Navaneethan U, Konjeti R) independently conducted a comprehensive search of the Cochrane library, PUBMED, Google scholar, Scopus, National Institutes of Health, meta-register of controlled trials and published proceedings from major Gastroenterology journals and meetings until February 2013. The search was conducted using the key words endoscopic retrograde cholangiopancreatography, ERCP, precut, cannulation, needle-knife, papillotomy, sphincterotomy, fistulotomy. All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles. In the case of studies with incomplete information, the principal authors were contacted to obtain additional data.

We applied the following inclusion criteria for identifying studies for our analysis: (1) prospective RCTs comparing cannulation techniques: "early precut" group in which precutting was done early during the procedure and the "persistent attempts" group in which persistent attempts were made with standard cannulation; and (2) Comparison of major complications (PEP, cholangitis, ERCP-related bleeding and perforation) between the two groups. Our outcomes of interest were PEP, overall complication rates and cannulation rates. Prospective non-randomized studies and retrospective studies were excluded from our meta-analysis.

Quality assessment

The quality of the studies was assessed according to quality criteria (Table 1). Simple and direct questions were organized to investigate each quality measure by two independent investigators (Navaneethan U, Konjeti R).

Statistical analysis

Data was extracted by two independent reviewers with

Table 1 Study quality characteristics of randomized controlled trials

Ref.	Were patients randomized	Was generation of allocation sequence adequate	Eligibility criteria mentioned	Both patients and clinicians blinded	Participants baseline characteristics similar in both groups	Treatment allocation concealed	Study adequately powered to asses significant clinical outcome
Tang *et al*[10]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	No
Zhou *et al*[19]	Yes	Yes	Partially	Partially fulfilled	Yes	Yes	N/A
de Weerth *et al*[12]	Yes	N/A	Yes	Partially fulfilled	Yes	N/A	N/A
Khatibian *et al*[18]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	Partially
Manes *et al*[20]	Yes	Yes	Yes	Partially fulfilled	Yes	N/A	No
Cennamo *et al*[11]	Yes	Yes	Yes	Partially fulfilled	Yes	Yes	No
Swan *et al*[14]	Yes	Yes	Yes	Yes	Yes	Yes	No

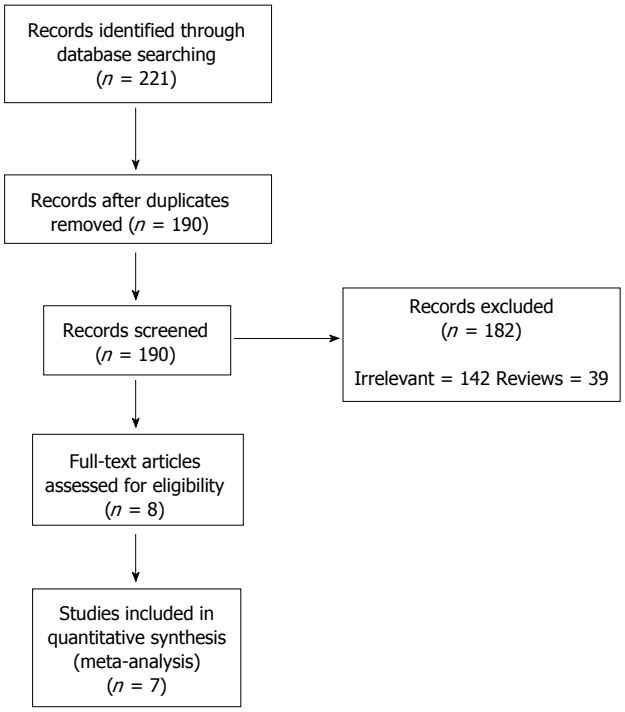


Figure 1 Flow chart demonstrating the literature search for the meta-analysis.

discrepancies settled by a third investigator (Sanaka MR). We performed the review and meta-analyses following the recommendations of The Cochrane Collaboration[15]. The analyses were performed using RevMan version 5.1. Binary outcomes were expressed as relative risks (RR) and continuous outcomes as median or mean difference, with 95%CI. Data was analyzed by fixed or random-effects model depending on heterogeneity[16]. Regression analyses were performed to estimate funnel plot asymmetry[17]. In our analysis, heterogeneity was explored by the chi-square test, with significance set at a P value of 0.05, and measured by I^2[15]. A sensitivity analysis using random effects models for the overall deep-biliary cannulation rate was also performed.

RESULTS

Literature search and characteristics of included studies

Two-hundred and twenty one potentially relevant studies were identified by our primary search of the electronic databases for published work on the subject. Of these studies, 214 were excluded after further review of the title and abstract for irrelevant topics, duplication of the reports, prospective non-RCTs or not meeting inclusion criteria. After careful review, 7 RCTs were eligible for meta-analysis. The detailed process of this literature search is shown in Figure 1. The characteristic of each included study is shown in Table 2.

The study quality characteristics are discussed in Table 1. The recent RCT by Swan *et al*[14] was a blinded study. Immediate precut was performed in two studies in patients randomized to precut arm without any previous cannulation attempts[12,18]. In the remaining 5 RCTs, pre-cut randomized patients had 5-12 min of biliary cannulation attempts[10,11,14,19,20], or if there was three accidental pancreatic duct cannulations[11,19]. In the study by Swan *et al*[14], endoscopists placed a pancreatic stent (Zimmon; Cook Medical, Bloomington, IN; single pigtail, 2-5 cm 5F) before pre-cut sphincterotomy if the PD had been cannulated at least twice. If the PD had not been cannulated during the biliary cannulation attempt(s), a PD stent was not placed. There was no significant difference in the use of PD stents between the 2 randomized groups; 15 of 34 (44%) in the persistent attempts group and 23 of 39 (59%) in the pre-cut sphincterotomy arm. Similarly, there was no statistical difference in the use of PD stents in the successful continued cannulation group *vs* those in the continued cannulation group who required crossover to pre-cut sphincterotomy; 5 of 12 (41%) *vs* 10 of 22 (45%) respectively. In rest of the studies pancreatic stent placement was not implemented in both the randomized arms. Six studies[10-12,14,18,20] defined procedure-related complications.

The techniques employed for cannulation and precut were different in the included studies (Table 3). In the persistent attempts group, the wire-guided technique was implemented to achieve deep biliary cannulation in most of the studies[11,12,14,18].

Comparative pancreatitis and overall complication rates between early precut and persistent attempt groups

Seven RCTs compared the overall complication rates (Table 1). The baseline characteristics of the studies are presented in detail in Tables 1 and 2. In our meta-analysis (Figure 2A) including 7 studies, the overall complication rates including PEP, bleeding and perforation were

Table 2 Study characteristics of randomized controlled trials

Ref.	Country	Center involved	No. of patients screened	Patients allocated to early precut/persistent attempts
Tang *et al*[10]	Canada	Single center	642	32/30
Zhou *et al*[19]	China	Single center	948	43/48
de Weerth *et al*[12]	Germany	Single center	291	145/146
Khatibian et al[18]	Iran	Single center	242	106/112
Manes *et al*[20]	Italy	Multicenter	1654	80/78
Cennamo *et al*[11]	Italy	Single center	1078	36/110
Swan *et al*[14]	Australia	Single center	464	39/34

Table 3 Techniques of pre-cut in randomized controlled trials

Ref.	Technique used in persistent attempts group	Timing of early precut	Precut technique	Timing of persistent attempts
Tang *et al*[10]	Non-wire guided sphincterotome	Biliary cannulation failed within 12 min	Needle knife precut starting at orifice	Biliary cannulation failed within 15 min
Zhou *et al*[19]	Non-wire guided and wire guided sphincterotome	Biliary cannulation failed within 10 min or 3 unintended pancreatic duct cannulation	Needle knife precut starting at orifice and fistulotomy	Not available
de Weerth *et al*[12]	Wire guided sphincterotome	Immediate precut for direct bile duct access	Erlangen type sphincterotome on the papillary roof	Biliary cannulation failed within 10 min or 3 unintended pancreatic duct cannulation
Khatibian *et al*[18]	Wire guided sphincterotome	Immediate needle knife fistulotomy for direct CBD access	Needle knife fistulotomy	Biliary cannulation failed within 15 min
Manes *et al*[20]	Non-wire guided and wire guided sphincterotome	Biliary cannulation failed within 10 min	Needle knife fistulotomy	Biliary cannulation failed within 10 min
Cennamo *et al*[11]	Wire guided sphincterotome	Biliary cannulation failed within 5 min or 3 unintended pancreatic duct cannulation	Needle knife precut starting at orifice	Biliary cannulation failed within 20 min post randomization
Swan *et al*[14]	Wire guided sphincterotome	Biliary cannulation failed within 10 min	Needle knife precut starting from superior aspect of orifice	Biliary cannulation failed within 10 min post randomization

6.2% (30 cases out of 481 patients) in precut group and 6.9% (39 cases out of 558 patients) in persistent attempts group. The pooled analysis didn't show any statistically significant difference between the two groups with an OR 0.85 (95%CI: 0.51-1.41). As the pooled estimation didn't showed significant heterogeneity a fixed-effect model was used in this analysis. The risk of PEP was 3.9% (19 cases out of 481 patients) in precut group and 6.1 % (34 cases out of 558 patients) in the persistent attempts group (Figure 3A). Although a trend towards a lower incidence of PEP in the early precut groups was observed, the pooled analysis didn't show any statistically significant difference between the two groups with an OR 0.59 (95%CI: 0.32-1.07).

The bleeding rate was found to be 1.8% (9 cases out of 481) in precut group and 0.9 % (5 cases out of 558 patients) in the persistent attempts group. The perforation rate was found to be 0.4% (2 cases out of 481) in precut group and 0.18 % (1 case out of 558 patients) in persistent attempts group. An analysis for cholangitis as a complication was not done as rates were not reported in two studies. The numbers were very small to calculate the pooled OR for these complications separately.

Cannulation rates

The overall cannulation rate was found to be 90% in pre-cut sphincterotomy group and 86.3% in persistent attempts group. The pooled analysis didn't show any significant difference between the two groups with an OR 1.98 (95%CI: 0.70-5.65) (Figure 4A). Statistical tests did show the presence of between-study heterogeneity and as such a random effects model was used to account for this heterogeneity.

Publication bias

Visual inspection of funnel plots in Figure 5 (for overall complications and post-ERCP pancreatitis) further confirms that publication bias is not a major determinant in this meta-analysis.

Subgroup analysis

In two studies included in our meta-analysis, pre-cut was performed even without attempts at cannulation with the standard approach[12,18]. The other studies had varying periods of cannulation attempts before randomization, reflecting real clinical practice. After excluding the two studies in which direct pre-cut was performed, the results were unchanged (Figure 2B, 3B and 4B).

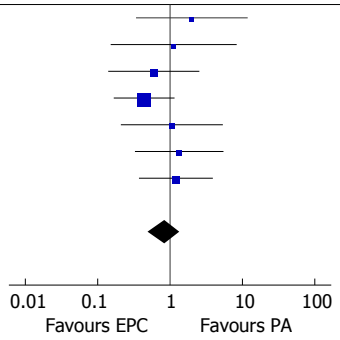
DISCUSSION

Despite advances in ERCP, failure of biliary cannulation and PEP remain two major issues where room for improvement exists. In experienced hands, successful

A

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	4	32	2	30	5.6%	2.00 [0.34, 11.82]	2005
Zhou 2006	2	43	2	48	5.5%	1.12 [0.15, 8.33]	2006
De Weerth 2006	3	145	5	146	15.0%	0.60 [0.14, 2.54]	2006
Khatibian 2008	3	106	3	112	8.7%	1.06 [0.21, 5.36]	2008
Manes 2008	7	80	14	78	39.8%	0.44 [0.17, 1.15]	2008
Cennamo 2009	3	36	7	110	9.7%	1.34 [0.33, 5.47]	2009
Swan 2013	8	39	6	34	15.7%	1.20 [0.37, 3.90]	2013
Total (95%CI)		481		558	100.0%	0.85 [0.51, 1.41]	
Total events	30		39				

Heterogeneity: χ^2 = 3.80, df = 6 (P = 0.70); I^2 = 0%
Test for overall effect: Z = 0.64 (P = 0.53)



B

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	4	32	2	30	7.3%	2.00 [0.34, 11.82]	2005
Zhou 2006	2	43	2	48	7.3%	1.12 [0.15, 8.33]	2006
Manes 2008	7	80	14	78	52.2%	0.44 [0.17, 1.15]	2008
Cennamo 2009	3	36	7	110	12.8%	1.34 [0.33, 5.47]	2009
Swan 2013	8	39	6	34	20.5%	1.20 [0.37, 3.90]	2013
Total (95%CI)		230		300	100.0%	0.87 [0.49, 1.56]	
Total events	24		31				

Heterogeneity: χ^2 = 3.49, df = 4 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

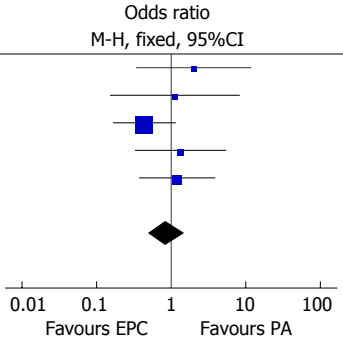
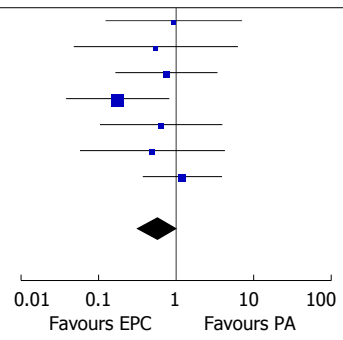


Figure 2 Overall complications. A: Overall complication rates of the two groups are shown in forest plot. The overall complication rates, considering pancreatitis, perforation, bleeding, and cholangitis rates, were 6.2% (30 cases out of 481 patients) in precut group and 6.9% (39 cases out of 558 patients) in persistent attempts group. The pooled analysis did not show any statistically significant difference between the two groups with an OR 0.85 (95%CI: 0.51-1.41); B: The overall complication rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

A

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	2	32	2	30	6.6%	0.93 [0.12, 7.08]	2005
Zhou 2006	1	43	2	48	6.3%	0.55 [0.05, 6.26]	2006
De Weerth 2006	3	145	4	146	13.4%	0.75 [0.16, 3.41]	2006
Khatibian 2008	2	106	11	112	36.0%	0.18 [0.04, 0.82]	2008
Manes 2008	2	80	3	78	10.2%	0.64 [0.10, 3.94]	2008
Cennamo 2009	1	36	6	110	9.9%	0.50 [0.06, 4.26]	2009
Swan 2013	8	39	6	34	17.5%	1.20 [0.37, 3.90]	2013
Total (95%CI)		481		558	100.0%	0.59 [0.32, 1.07]	
Total events	19		34				

Heterogeneity: χ^2 = 4.14, df = 6 (P = 0.66); I^2 = 0%
Test for overall effect: Z = 1.75 (P = 0.08)



B

Study or subgroup	EPC Events	EPC Total	PA Events	PA Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Tang 2005	2	32	2	30	13.2%	0.93 [0.12, 7.08]	2005
Zhou 2006	1	43	2	48	12.5%	0.55 [0.05, 6.26]	2006
Manes 2008	2	80	3	78	20.1%	0.64 [0.10, 3.94]	2008
Cennamo 2009	1	36	6	110	19.5%	0.50 [0.06, 4.26]	2009
Swan 2013	8	39	6	34	34.6%	1.20 [0.37, 3.90]	2013
Total (95%CI)		230		300	100.0%	0.83 [0.39, 1.78]	
Total events	14		19				

Heterogeneity: χ^2 = 0.81, df = 4 (P = 0.94); I^2 = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

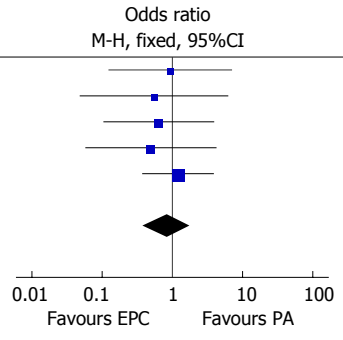


Figure 3 Overall post-endoscopic retrograde cholangiopancreatography pancreatitis. A: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis rates of the two groups are shown in Forest plot. The risk for post-ERCP pancreatitis was 3.9% (19 cases out of 481 patients) in precut group and 6.1 % (34 cases out of 558 patients) in the persistent attempts group. The pooled analysis did not show any statistically significant difference between the two groups with an OR 0.59 (95%CI: 0.32-1.07); B: The overall post-ERCP pancreatitis rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

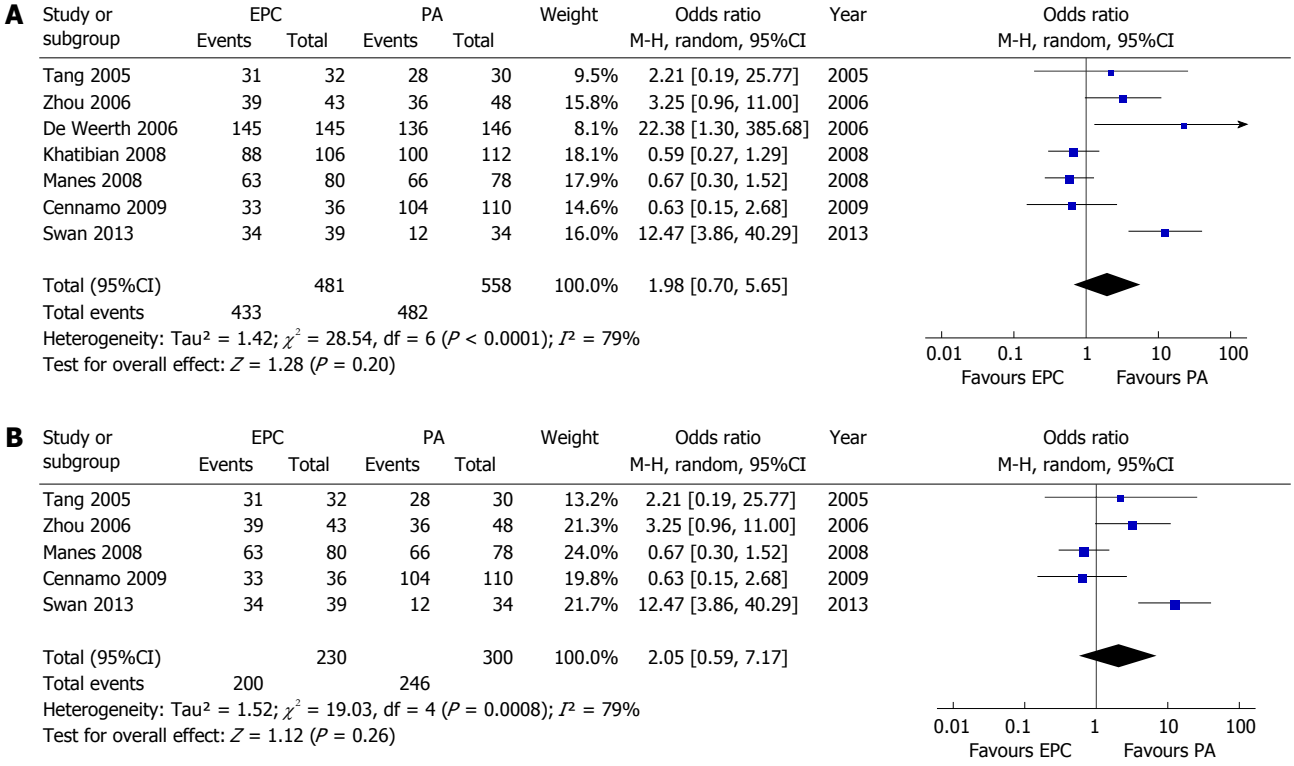


Figure 4 Overall cannulation rates. A: Cannulation rates of the two groups are shown in Forest plot. The overall cannulation rate was found to be 90% in pre-cut sphincterotomy group and 86.3% in persistent attempts group. The pooled analysis did not show any significant difference between the two groups with an OR 1.98 (95%CI: 0.70-5.65); B: The overall cannulation rates after excluding studies where direct pre-cut was performed. The results were unchanged. EPC: Early pre cut; PA: Persistent attempts.

biliary cannulation is achieved in over 90% of patients. In 5%-10% of patients, biliary cannulation is difficult for which various methods have been advocated in the literature. Pre-cut sphincterotomy is a valuable technique to achieve biliary access when conventional techniques fail. However, the timing of this procedure is controversial with some literature suggesting that early use of precut sphincterotomy may be preferable to persistent attempts at cannulation with standard approach. In older literature the use of pre-cut technique has been associated with higher rates of PEP, discouraging its use[9,21].

Past studies assessing the association between PEP and precut sphincterotomy have shown seemingly contradictory results. Two prospective studies[22,23] and one meta-analysis[24], suggested a positive association between precut sphincterotomy and risk of PEP, while in 3 prospective studies there was lack of an independent association between pre-cut sphincterotomy and risk of PEP[10,11,20]. There are multiple case series showing similar complication rates for precut and standard sphincterotomy techniques[25,26]. The discrepancy among these studies may be due to factors such as varying experience among endoscopists, varying precut timing during the procedure, different patient populations and use of prophylactic pancreatic stents. Even among the studies included in this meta-analysis, prophylactic pancreatic stents were used only in one study[14]. Also, non-steroidal anti-inflammatory drugs such as indomethacin were not used in any of the studies included in this analysis. Thus, these results do not entirely mirror the current clinical practice of using either pancreatic stents and/or non-steroidal anti-inflammatory medications when performing difficult biliary cannulation during ERCP.

Our meta-analysis, demonstrated that early pre-cut sphincterotomy does not increase the risk of PEP. In fact, although not statistically significant, there was a trend towards a lower risk of PEP with early use of pre-cut sphincterotomy compared to persistent attempts at cannulation. The possible increased risk of PEP with persistent standard cannulation may be because of mechanical damage to the papilla and the pancreatic sphincter[27-33].

In two studies included in our meta-analysis, pre-cut was performed even without attempts at cannulation with the standard approach[12,18]. The other studies had varying periods of cannulation attempts before randomization, reflecting real clinical practice. After excluding the two studies in which direct pre-cut was performed, the results were unchanged. However the question of when to proceed to pre-cut in patients with difficult biliary cannulation has not been studied in RCTs thus far. The most recent RCT included in this meta-analysis suggested that the risk of PEP increased with more than 6-7 attempts at cannulation suggesting the possible threshold to proceed to pre-cut sphincterotomy[14].

In addition to PEP; bleeding[8] and perforation[9] are other complications associated with precut techniques. In this study the bleeding rate was found to be 1.8% in the

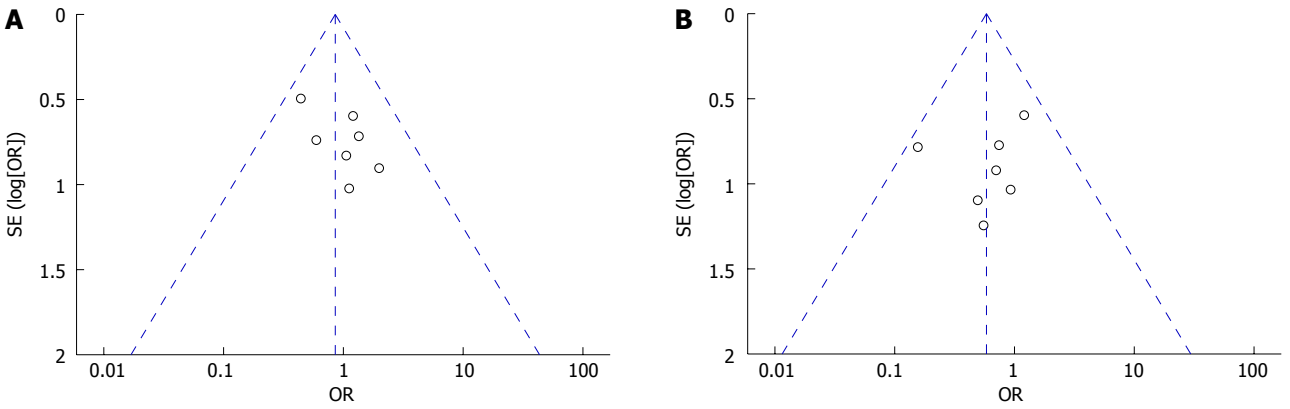


Figure 5 Funnel plot of overall complication and post-endoscopic retrograde cholangiopancreatography pancreatitis rates confirms that publication bias is not a major determinant of pooled diagnostic accuracy in this meta-analysis.

precut group and 0.9% in the persistent attempts group. The perforation rate was found to be 0.4% in the precut group and 0.2% in persistent attempts group. Although we did not detect any statistically significant difference in bleeding and perforation rates between the two groups, the numbers suggest that a larger patient population may have detected possible subtle differences.

The timing of pre-cut remains controversial. Of the seven studies, Tang *et al*[10] study did not include late pre-cut in their analysis. The study by Cennamo *et al*[11] study included early and late pre-cut subgroup and sub-analysis did not showed any difference ($P = 0.25$). The study by de Weerth *et al*[12] included both early and late pre-cut, but the authors that there was no difference in the complications. However, no data was available to do sub-analysis. The other two studies by Manes *et al*[20] and Swan *et al*[14] included patients in early and late pre-cut, but the authors mentioned that subgroup analysis did not show any statistical difference in the post-ERCP complication rates. The other two studies did not separate into early and late pre-cut group for doing a sub-analysis.

The other issue is the use of pancreatic duct (PD) stents one of the studies included in the meta-analysis. In the study by Swan *et al*[14], pancreatic duct (PD) stents were used. There was no significant difference in the use of PD stents between the 2 randomized groups, 15 of 34 (44%) in the standard cannulation arm and 23 of 39 (59%) in the NKS arm. Similarly, there was no statistical difference in the use of PD stents in the standard cannulation group *vs* those in the standard cannulation arm who required crossover to NKS, 5 of 12 (41%) *vs* 10 of 22 (45%). Multivariate analysis of risk factors for PEP showed clearly that PD stent insertion did not affect the results. Hence it is unlikely that use of PD stents affected our results.

It is important to emphasize that precut sphincterotomy, although did not increase the complication rate should be done only for therapeutic ERCP with failed guidewire cannulation. Certain patients are considered to be high-risk for development of PEP. In a meta-analysis, patients with suspected sphincter of Oddi dysfunction (RR = 4.09, 95%CI: 3.37-4.96, $P < 0.001$), female gender (RR 2.23, 95%CI: 1.75-2.84, $P < 0.001$), and those with a previous history of pancreatitis (RR 2.46, 95%CI: 1.93-3.12, $P < 0.001$) were at high risk; additional procedure-related risk factors for PEP were pancreatic sphincterotomy (RR = 2.71, 95%CI: 2.02-3.63, $P < 0.001$) and pancreatic injection (RR = 2.2, 95%CI: 1.6-3.01, $P < 0.001$)[34].

Strengths of this meta-analysis are the inclusion of all RCTs to date. In addition, statistical analysis did not show any significant heterogeneity among the included studies. Furthermore, all included studies reported similar demographic data. However, as all ERCP procedures were done by experienced endoscopists in referral medical centers, the results may not be applicable to community setting practice. Also, the techniques employed for cannulation and precut were different in the included studies. The possible significance of this in altering or modifying the outcomes remains unclear, considering that different techniques may offer different incidence of complications.

To conclude, our study confirms that pre-cut sphincterotomy is a safe and effective strategy when used by experienced biliary endoscopists and does not increase the risk of PEP. However, the exact timing for implementing pre-cut in patients with difficult cannulation remains uncertain and further RCTs employing the time line along with use of pancreatic stents and/or non-steroidal anti-inflammatory medications are required.

COMMENTS

Background

The presumed risks and morbidity associated with needle knife sphincterotomy (NKS) in patients with failed routine cannulation, particularly risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) has discouraged use of this technique in patients with difficult biliary access. The authors sought to perform an updated meta-analysis to study the differences in cannulation rates, PEP and overall complication risk between early pre-cut sphincterotomy and persistent attempts at cannulation, taking the new randomized study into consideration.

Research frontiers

An earlier meta-analysis demonstrated that early precut sphincterotomy reduces PEP risk but not the overall complication rate or cannulation success.

Subsequent to this publication, another RCT has been published.

Innovations and breakthroughs

Based on this meta-analysis, pre-cut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates.

Applications

Although pre-cut is demonstrated as safe, the exact timing for implementing pre-cut in patients with difficult cannulation remains uncertain and further studies should employ the time line along with use of pancreatic stents and/or non-steroidal anti-inflammatory medications to determine the optimal approach for biliary cannulation.

Terminology

ERCP has been widely used for treatment of a variety of biliary disorders and cannulation of the bile duct remains one of the most important steps for successful therapeutic endoscopy. Precut sphincterotomy, also referred to as NKS, has been advocated in situations where routine biliary cannulation has been unsuccessful.

Peer review

This paper confirms that precut sphincterotomy is not more harmful that persistent attempts of cannulation of the papilla in terms of pancreatitis and other complications. It is well done and the inclusion criteria are correct and well defined.

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META-ANALYSIS

Systematic review of oncological outcomes following laparoscopic *vs* open total mesorectal excision

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Abstract

AIM: To systematically analyze the randomized trials comparing the oncological and clinical effectiveness of laparoscopic total mesorectal excision (LTME) vs open total mesorectal excision (OTME) in the management of rectal cancer.

METHODS: Published randomized, controlled trials comparing the oncological and clinical effectiveness of LTME vs OTME in the management of rectal cancer were retrieved from the standard electronic medical databases. The data of included randomized, controlled trials was extracted and then analyzed according to the principles of meta-analysis using RevMan® statistical software. The combined outcome of the binary variables was expressed as odds ratio (OR) and the combined outcome of the continuous variables was presented in the form of standardized mean difference (SMD).

RESULTS: Data from eleven randomized, controlled trials on 2143 patients were retrieved from the electronic databases. There was a trend towards the higher risk of surgical site infection (OR = 0.66; 95%CI: 0.44-1.00; z = 1.94; $P < 0.05$), higher risk of incomplete total mesorectal resection (OR = 0.62; 95%CI: 0.43-0.91; z = 2.49; $P < 0.01$) and prolonged length of hospital stay (SMD, -1.59; 95%CI: -0.86--0.25; z = 4.22; $P < 0.00001$) following OTME. However, the oncological outcomes like number of harvested lymph nodes, tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the clinical outcomes such as operative complications, anastomotic leak and all-cause mortality were comparable between both approaches of mesorectal excision.

CONCLUSION: LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary rectal cancer in both short term and long term follow ups.

Key words: Total mesorectal excision; Anterior resection; Abdominoperineal resection; Rectal cancer; Oncological outcomes

Core tip: Based upon the findings of this systematic review of eleven randomized trial on 2143 patients of rectal cancer, there is a higher risk of surgical site infection, higher risk of incomplete total mesorectal resection and prolonged length of hospital stay following open total mesorectal excision (OTME) compared to laparoscopic total mesorectal excision (LTME). The number of harvested lymph nodes, tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the operative complications, anastomotic leak and mortality were compa-

rable between LTME and OTME. LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary resectable rectal cancer.

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INTRODUCTION

Colorectal cancer is one of the major causes of mortality among western population[1,2]. Radical resection of the rectum in the form of anterior resection and abdominoperineal resection has been advocated for many decades to achieve highest level of oncological clearance and overall survival[3-8]. The introduction of total mesorectal excision in the management of rectal cancer has also enhanced survival and reduced the risk of local recurrence[9-14] because it achieves complete excision of the rectum together with its lymphatics and lymph nodes. Therefore, total mesorectal excision has become gold standard surgical strategy to treat rectal malignancies[10,11]. Laparoscopic total mesorectal excision (LTME) offers several advantages over conventional and orthodox open total mesorectal excision (OTME) such as reduced blood loss, faster recovery, reduced postoperative pain score, early feeding, early return to normal activities and a reduced risk of postoperative complications[12-16]. However, these advantages of LTME can only be availed optimally by colorectal surgeons when its oncological viability is proven on scientific grounds. One would assume that LTME for rectal cancer should offer survival and recurrence similar to OTME[17-19]. In addition, several studies have also reported the concerns towards LTME requiring longer duration of operation, needing extensive learning curve for colorectal surgeons, particularly junior colorectal trainees and cost implications of the procedure[20,21]. Aforementioned three limitations of LTME can be offset if its oncological and clinical adequacy matches the OTME. The objective of this article is to explore the oncological safety and clinical effectiveness of the LTME comparing to OTME based upon the principles of meta-analysis.

MATERIALS AND METHODS

Electronic data sources and their search planning

In order to obtain pertinent studies, a search of common medical electronic databases such as MEDLINE, EMBASE, and the Cochrane library for randomized, controlled trials was conducted and screened according to PRIMSA flow chart (Figure 1). The MeSH terms published in the Medline library relevant to the oncological and clinical outcomes following LTME or OTME were used to hit upon the relevant trials. No limits for language, gender, sample size and place of study origin were entered for the search in the database search engine. Boolean operators (AND, OR = NOT) were additionally used to narrow and widen the results of potentially usable studies. The titles of the published articles from the search results were examined closely and determined to be suitable for potential inclusion into this review article. The reference list from selected articles was also examined as a further search tool to discover additional trials.

Selection criteria for included trials

For inclusion in this meta-analysis, a study had to fulfill the following criteria: (1) randomized, controlled trial; (2) comparison between LTME and OTME; (3) evaluation of a well-defined primary outcome; (4) main outcome measures reported preferably as an intention-to-treat (ITT) analysis; and (5) trials on surgical patients those have endoscopically and histologically proven rectal cancer.

Data abstraction from included trials

Two independent reviewers using a predefined meta-analysis form abstracted relevant data of oncological and clinical outcomes following LTME and OTME from each study which resulted in high and satisfactory interobserver agreement. The extracted data contained name of the publishing authors, title of the published study, journal in which the study was published, country and year of the study, intervention protocol in the both limbs of the trial, method by which LTME and OTME was performed, testing sample size (with sex differentiation if applicable), the number of patients receiving each regimen and within the group the number of patients who succeeded and the number of patients who failed the allocated treatment, the patient compliance rate in each group, the number of patients reporting complications and the number of patients with absence of complications in each arm of the trial. After completing the data abstraction the two independent reviewers discussed the data related results and, if discrepancies were present, a consensus was reached.

Statistical analysis

The software package RevMan 5.2[22,23], provided by the Cochrane Collaboration, was used for the statistical analysis. The odds ratio (OR) with a 95%CI was calculated for binary data, and the standardized mean difference (SMD) with a 95%CI was calculated for continuous variables. The random-effects model[24,25] was used to calculate the combined outcomes of both binary and continuous variables. Heterogeneity was explored using the χ^2 test, with significance set at $P < 0.05$, and was quantified[26] using I^2, with a maximum value of 30 percent identifying low heterogeneity[26]. The Mantel-Haenszel method was used for the calculation of OR under the random effect models[27]. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either

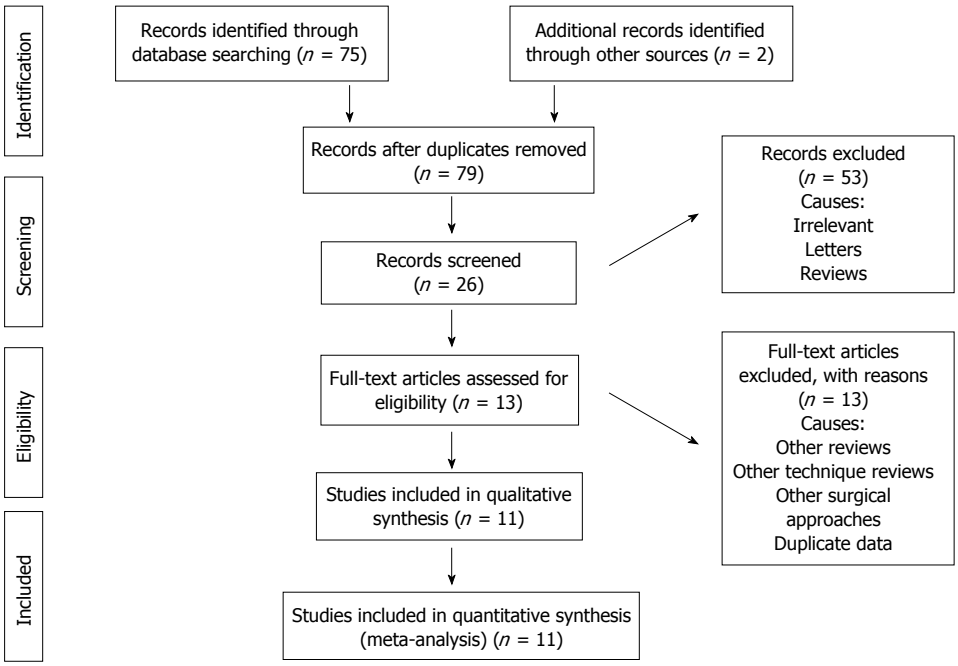


Figure 1 PRISMA flow diagram.

the treatment or control group, according to the method recommended by Deeks *et al*[28]. If the standard deviation was not available, then it was calculated according to the guidelines of the Cochrane Collaboration[22]. This process involved assumptions that both groups had the same variance, which may not have been true, and variance was either estimated from the range or from the *P*-value. The estimate of the difference between both techniques was pooled, depending upon the effect weights in results determined by each trial estimate variance. A forest plot was used for the graphical display of the results. The square around the estimate stood for the accuracy of the estimation (sample size), and the horizontal line represented the 95%CI. The methodological quality of the randomized, controlled trials was assessed using the published guidelines of Jaddad *et al*[29] and Chalmers *et al*[30]. Based on the quality of the included randomized, controlled trials, the strength and summary of the evidence was further evaluated by GradePro®[31], a tool provided by the Cochrane Collaboration.

Outcomes

Incidence of complete TME was analysed as primary endpoint in this study. Secondary endpoints included circumferential resection margin (CRM) positivity, number of harvested lymph nodes, mortality, morbidity, anastomotic leak, surgical site infection and length of hospital stay.

RESULTS

Eleven randomized, controlled trials encompassing 2143 patients[32-42] were retrieved from the electronic databases. There were 1189 patients in the LTME group and 954 patients in the OTME group. The characteristics of the included trials are given in Table 1. The salient features and treatment protocols adopted in the included trials are given in Table 2. We used the data from one publication only from two published articles[35,36] of same randomized, controlled trial in order to avoid the duplication of data.

Methodological quality of included studies

Based upon the published guidelines of Jaddad *et al*[29] and Chalmers *et al*[30] the quality of majority of included randomized, controlled trials[33,35-41] was considered good. Only three[32,34,42] included trials were scored of low quality due to the absence of adequate randomisation technique, power calculations, blinding, adequate concealment process and lack of intention-to-treat analysis. Based on the quality of included trials, the strength and summary of the evidence analyzed on GradePro®[31] is given in Figure 2. The reported quality variables of included trials are given in Table 3.

Risk of incomplete total mesorectal excision

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 2.41$, $\gamma = 3$, ($P = 0.49$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.62; 95%CI: 0.43-0.91; z = 2.49; $P < 0.01$; Figure 3A), the risk of incomplete total mesorectal excision was higher following OTME compared to LTME.

Risk of positive circumferential resection margins

There was no heterogeneity [$Tau^2 = 0.0$, $\chi^2 = 1.80$, $\gamma = 7$, ($P = 0.97$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.98; 95%CI: 0.63, 1.51; z = 0.10; $P = 0.71$; Figure 3B), the risk of positive circum-

Table 1 Characteristics of included trials

Ref.	Year	Country	Age (yr)	Gender (M:F)	Follow up (mo)	Rectal cancer details	Procedure
Araujo *et al*[32]	2003	Brazil				Lower rectal cancer with neoadjuvant chemoradiotherapy	Abdominoperineal resection
LTME			59.1	9:4	47.2		
OTME			56.4	10:5	47.2		
Baraga *et al*[33]	2007	Italy				Adenocarcinoma of the rectum suitable for resection with neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			62.8 ± 12.6	55:28	53.6		
OTME			65.3 ± 10.3	64:21			
Gong *et al*[34]	2012	China				Lower and mid rectal adenocarcinoma without neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			58.4 ± 13.6	1.3:1	21 (9-56)		
OTME			59.6 ± 9.4	1.29:1			
Guillou *et al*[35]	2005	United				Adenocarcinoma of left colon and rectum	Anterior resection and Abdominoperineal resection
LTME		Kingdom	69 ± 11	44% female	3		
OTME			69 ± 12	46% female	3		
Jayne *et al*[36]	2007	United				Adenocarcinoma of left colon and rectum	Anterior resection and Abdominoperineal resection
LTME		Kingdom	69 ± 11	44% female	36.5		
OTME			69 ± 12	46% female	36.5		
Kang *et al*[37]	2010	South				Lower and mid rectal adenocarcinoma with neoadjuvant chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME		Korea	57.8 ± 11.1	110:60	3		
OTME			59.1 ± 9.9	110:60	3		
Lujan *et al*[38]	2009	Spain				Upper rectal adenocarcinoma Mid or low rectal adenocarcinoma cT3N0-2 stage Preoperative chemoradiotherapy	Anterior resection and Abdominoperineal resection
LTME			67.8 ± 12.9	62:39	32.8		
OTME			66 ± 9.9	64:39	34.1		
Ng *et al*[39]	2008	Hong				Lower rectal cancer within 5 cm of the anal verge	Abdominoperineal resection
LTME		Kong	63.7 ± 11.8	31:20	90.1		
OTME			63.5 ± 12.6	30:18	87.2		
Ng *et al*[40]	2009	Hong				Upper rectal adenocarcinoma Preoperative chemoradiotherapy	Anterior resection
LTME		Kong	66.5 ± 11.9	37:39	112.5		
OTME			65.7 ± 12	48:29	108.8		
Ng *et al*[41]	2013	Hong				Rectal adenocarcinoma located between 5 and 12 cm from the anal verge. None of the included patient had neoadjuvant treatment	Sphincter sparing total mesorectal excision
LTME		Kong	60.2 ± 11.3	24:16	84.6		
OTME			62.1 ± 12.6	22:18	92.7		
Zhou *et al*[42]	2004	China				Low rectal adenocarcinoma Intraperitoneal and 1.5 to 8 cm from the dentate line Dukes D with local infiltration Anal sphincter sparing	Anterior resection
LTME			26-85(44)	43:46			
OTME			30-81(45)	46:36	1-16		

LTME: Laparoscopic total mesorectal excision; OTME: Open total mesorectal excision; M: Male; F: Female.

ferential resection margins was similar following both approaches.

Number of harvested lymph nodes

There was significant heterogeneity [$Tau^2 = 0.12$, $\chi^2 = 48.61$, $\gamma = 8$, ($P > 0.00001$); $I^2 = 84\%$] among included studies. In the random effects model (SMD, -0.14; 95%CI: -0.40-0.12; z = 1.08; $P < 0.28$; Figure 3C), the number of harvested lymph nodes following both procedures was statistically similar.

Recurrence

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 4.57$, $\gamma = 7$, ($P = 0.71$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.82; 95%CI: 0.59-1.15; z = 1.16; $P = 0.24$; Figure 3D), the risk of rectal cancer recurrence was similar between both types of excisions.

Duration of hospital stay

There was significant heterogeneity [$Tau^2 = 0.21$, $\chi^2 = 82.18$, $\gamma = 9$, ($P < 0.00001$); $I^2 = 89\%$] among included studies. In the random effects model (SMD, -1.59; 95%CI: -0.86--0.25; z = 4.22; $P < 0.00001$; Figure 3E), the length of hospital stay was shorter following LTME compared to OTME.

Short term and long term operative complications

There was significant heterogeneity [$Tau^2 = 0.30$, $\chi^2 = 28.55$, $\gamma = 9$, ($P < 0.0008$); $I^2 = 68\%$] among included studies. In the random effects model (OR = 0.69; 95%CI: 0.43, 1.08; z = 1.62; $P = 0.11$; Figure 3F), the incidence of complications was similar following both approaches of rectal cancer resection.

Overall mortality

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 0.45$, $\gamma = 3$, ($P = 0.93$); $I^2 = 0\%$] among included studies. In the random effects model (OR = 0.70; 95%CI: 0.41-1.18; z = 1.33; $P = 0.18$; Figure 3G), the incidence of overall mortality was similar following LTME and OTME.

Anastomosis leak

There was no heterogeneity [$Tau^2 = 0.00$, $\chi^2 = 6.18$, $\gamma = 7$, ($P = 0.52$); $I^2 = 0\%$] among included studies. In the

Table 2 Treatment protocol adopted in included trials

Ref.	LTME group	OTME group
Araujo *et al*[32]	4 × 10/11 mm ports were used with some variations Trendelenburg position Harmonic scalpel for dissection Lateral to medial dissection Endoscopic stapler for inferior mesenteric pedicle division Colonic division by endostapler Standard technique of colostomy construction Standard perineal phase, dissection and closure	Procedure protocol was not reported
Baraga *et al*[33]	Intracorporeal vascular pedicle division, rectal mobilization and division, and anastomosis Anastomosis by Knight-Griffen technique Selective defunctioning stoma placement	Procedure protocol was not reported Selective defunctioning stoma placement
Gong *et al*[34]	4 ports were used with some variations Medial to lateral dissection Clips to secure inferior mesenteric pedicle Rectal division by endostapler Standard technique of colostomy construction Standard perineal phase, dissection and closure	Standard open TME Sphincter preserving surgery in both groups in selective patients No defunctioning stoma in both groups
Guillou *et al*[35]	Detailed procedure protocol was not reported	Detailed procedure protocol was not reported
Jayne *et al*[36]	3 yr results of Guillou *et al*[35] Detailed procedure protocol was not reported	3 yr results of Guillou *et al*[35] Detailed procedure protocol was not reported
Kang *et al*[37]	Six weeks after completion of chemoradiotherapy 5 ports were used Clips to secure inferior mesenteric pedicle Splenic flexure was mobilized in all patients Harmonic scalpel or diathermy for dissection Rectal division by endostapler Colorectal anastomosis by double staple technique or by trans-anal suture All patients had defunctioning stoma	Detailed procedure protocol was not reported Sphincter preservation in selective patients in both groups
Lujan *et al*[38]	4 ports were used Stapled side to end colorectal or colo-anal hand sewn anastomosis Selective defunctioning stoma placement	Lloyd-Davis position and midline laparotomy Stapled side to end colorectal or colo-anal hand sewn anastomosis Sphincter preservation in selective patients in both groups Selective defunctioning stoma placement
Ng *et al*[39]	4 or 5 ports were used Staplers for vascular pedicle and bowel transection Standard perineal resection	Standard open abdominoperineal resection
Ng *et al*[40]	Protocol of the laparoscopic resection technique was not reported	Protocol of the open resection technique was not reported
Ng *et al*[41]	Lateral to medial mobilization Endostapler for rectal and vascular pedicle transection Electrocautry was used to dissect through "Holy plane" for total mesorectal resection Splenic flexure mobilization in selective patients Anastomosis by double stapling technique Defunctioning stoma in selective patients	Protocol of the open resection technique was not reported
Zhou *et al*[42]	Lithotomy position with head down tilt Laparoscopy technique was not reported Intracorporeal anastomosis Endostapler for vascular and rectal transactions Harmonic scalpel was used for dissection No defunctioning stoma	Standard open total mesorectal excision previously published by Heald *et al*[10,11] Electrocautry was used for hemostasis No defunctioning stoma

TME: Total mesorectal excision; LTME: Laparoscopic total mesorectal excision; OTME: Open total mesorectal excision.

random effects model (OR = 0.92; 95%CI: 0.56-1.50; z = 0.33; P = 0.74; Figure 3H), the risk of colorectal anastomotic dehiscence was similar following both approaches.

Surgical site infection

There was significant no heterogeneity [Tau^2 = 0.07, χ^2 = 10.61, γ = 9, (P = 0.30); I^2 = 15%] among included studies. In the random effects model (OR = 0.66; 95%CI: 0.44-1.00; z = 1.94; $P < 0.05$; Figure 3I), the risk of surgical site infection was higher following OTME compared to LTME.

DISCUSSION

Based upon the findings of this largest ever systematic review of eleven randomized, controlled trial on 2143

All variables in LTME *vs* OTME for [health problem]

Patient or population: patients with [healith problem]

Settings:

Intervention: All variables in LTME *vs* OTME

Outcomes	Illustrative comparative risks[1] (95%CI) Assumed risk Control	 Corresponding risk All variables in LTME *vs* OTME	Relative effect (95%CI)	No of participants (students)	Quality of the evidence (GRADE)	Comments
Incidence of incomplete TME OR Follow-up: 3-12 mo	Study population 85 per 1000 Moderate 0 per 1000	54 per 1000 (38 to 78) 0 per 1000 (0 to 0)	OR = 0.62 (0.43 to 0.91)	1762 (10 studies)	Moderate	
Incidence of CRM positivity OR Follow-up: 3-112 mo	Study population 55 per 1000 Moderate 35 per 1000	54 per 1000 (36 to 81) 34 per 1000 (22 to 52)	OR = 0.98 (0.63 to 1.51)	1563 (8 studies)	Moderate	
Number of harvested lymph nodes Standardized mean difference Follow-up: 3-112 mo		The mean number of harvested lymph nodes in the intervention groups was 0.14 standard deviations lower (0.4 lower to 0.12 higher)		1633 (9 studies)	Moderate	SMD -0.14 (-0.4 to 0.12)
Recurrence OR Follow-up: 3-112 mo	Study population 131 per 1000 Moderate 133 per 1000	110 per 1000 (82 to 148) 112 per 1000 (83 to 150)	OR = 0.82 (0.59 to 1.15)	1422 (9 studies)	Moderate	
Length of stay Standardized mean difference Follow-up: 3-112 mo		The mean length of stay in the intervention groups was 0.55 standard deviation lower (0.86 ti 0.25 lower)		1762 (10 studies)	Moderate	SMD -0.55 (-0.86 to -0.25)
Short and long term complications OR Follow-up: 3-112 mo	Study population 430 per 1000 Moderate 503 per 1000	342 per 1000 (245 to 449) 411 per 1000 (303 to 522)	OR = 0.69 (0.43 to 1.08)	1762 (10 studies)	Moderate	
All cause mortality OR Follow-up: 3-112 mo	Study population 41 per 1000 Moderate 430 per 1000	29 per 1000 (17 to 48) 430 per 1000 (0 to 0)	OR = 0.7 (0.41 to 1.18)	1762 (10 studies)	Moderate	
Anastomosis leak rate OR Follow-up: 3-112 mo	Study population 46 per 1000 Moderate 34 per 1000	42 per 1000 (26 to 67) 31 per 1000 (19 to 50)	OR = 0.92 (0.56 to 1.5)	1732 (9 studies)	Moderate	
Surgical site infection OR Follow-up: 3-112 mo	Study population 99 per 1000 Moderate 117 per 1000	68 per 1000 (46 to 99) 80 per 1000 (55 to 117)	OR = 0.66 (0.44 to 1)	1762 (10 studies)	Moderate[2]	

[1]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes.
The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[2]No explanation was provided.

Figure 2 Strength and summary of the evidence analysed on GradePro®.

Table 3 Quality variables reported in the included trials

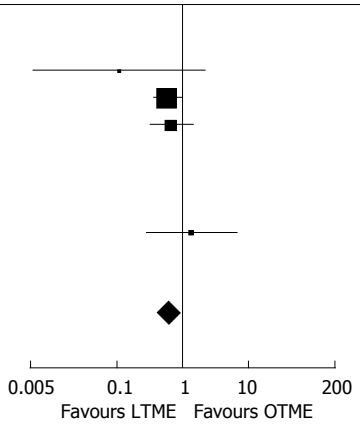
Ref.	Randomization	Power calculations	ITT	Blinding	Concealment
Araujo *et al*[32]	Not reported	Not reported	Not reported	Not reported	Not reported
Baraga *et al*[33]	Computer generated	Yes	Yes	Yes	Sealed blinded envelops
Gong *et al*[34]	Not reported	Not reported	Not reported	Not reported	Not reported
Guillou *et al*[35]	Random allocation with 2 to 1 ratio	Yes	Yes	Not reported	Allocation communicated by telephone
Jayne *et al*[36]	Random allocation with 2 to 1 ratio	Yes	Yes	Not reported	Allocation communicated by telephone
Kang *et al*[37]	Computer generated with block permutation	Yes	Yes	Yes	Allocation communicated by telephone
Lujan *et al*[38]	Computer generated	Yes	Yes	Yes	Sealed blinded envelops
Ng *et al*[39]	Computer generated random sequence	Yes	Yes	Yes	Concealed by theatre coordinator
Ng *et al*[40]	Computer generated	Yes	Yes	Not reported	Not reported
Ng *et al*[41]	Computer generated random sequence	Yes	Yes	Yes	Concealed by theatre coordinator
Zhou *et al*[42]	Not reported	Not reported	Not reported	Not reported	Not reported

ITT: Intention-to-treat.

A

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	0	15		Not estimable
Baraga 2007	0	83	0	85		Not estimable
Gong 2012	0	67	4	71	1.7%	0.11 [0.01, 2.10]
Guillou 2005	58	253	43	128	64.8%	0.59 [0.37, 0.94]
Kang 2010	14	170	20	170	27.7%	0.67 [0.33, 1.38]
Lujan 2009	0	101	0	103		Not estimable
Ng 2008	0	51	0	48		Not estimable
Ng 2009	0	76	0	77		Not estimable
Ng 2013	4	40	3	40	5.8%	1.37 [0.29, 6.56]
Zhou 2004	0	82	0	89		Not estimable
Total (95%CI)		936		826	100.0%	0.62 [0.43, 0.91]
Total events	76		70			

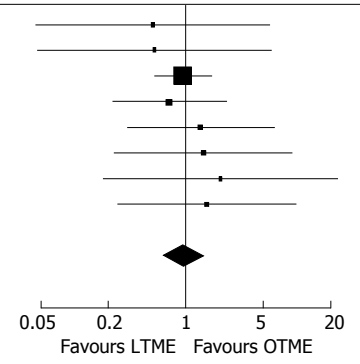
Heterogeneity: Tau^2 = 0.00; χ^2 = 2.41; df = 3 (P = 0.49); I^2 = 0%
Test for overall effect: Z = 2.45 (P = 0.01)



B

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Baraga 2007	1	83	2	85	3.2%	0.51 [0.05, 5.69]
Gong 2012	1	67	2	71	3.2%	0.52 [0.05, 5.90]
Guillou 2005	40	253	21	128	57.0%	0.96 [0.54, 1.70]
Kang 2010	5	170	7	170	13.9%	0.71 [0.22, 2.71]
Lujan 2009	4	101	3	103	8.2%	1.37 [0.30, 6,30]
Ng 2008	3	51	2	48	5.6%	1.44 [0.23, 9.00]
Ng 2009	2	76	1	77	3.2%	2.05 [0.18, 23.14]
Ng 2013	3	40	2	40	5.6%	1.54 [0.24, 9.75]
Total (95%CI)		841		722	100.0%	0.98 [0.63, 1.51]
Total events	59		40			

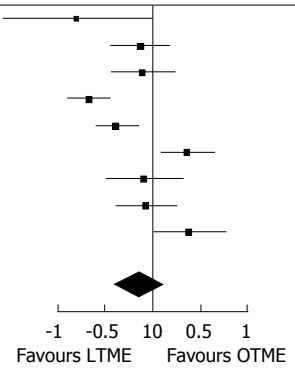
Heterogeneity: Tau^2 = 0.00; χ^2 = 1.80; df = 7 (P = 0.97); I^2 = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



C

Study or subgroup	LTME Mean	LTME SD	LTME Total	OTME Mean	OTME SD	OTME Total	Weight	Std. mean difference IV, random, 95%CI
Araujo 2003	5.5	7.8	13	11.9	7.8	15	6.2%	-0.80 [-1.57, -0.02]
Baraga 2007	12.7	7.3	83	13.6	6.9	85	11.8%	-0.13 [-0.43, 0.18]
Gong 2012	20.3	8.3	67	21.1	6.7	71	11.4%	-0.11 [-0.44, 0.23]
Guillou 2005	12	2.25	253	13.5	2.25	128	12.8%	-0.38 [-0.59, -0.17]
Kang 2010	17	2.5	170	18	2.75	170	12.8%	-0.38 [-0.59, -0.17]
Lujan 2009	13.63	6.26	101	11.57	5.1	103	12.1%	0.36 [0.08, 0.64]
Ng 2008	12.4	6.7	51	13	7	48	10.6%	-0.09 [-0.48, 0.31]
Ng 2009	11.5	7.9	76	12	7	77	11.6%	-0.07 [-0.38, 0.25]
Ng 2013	17.7	8.4	82	14.8	5.6	40	10.8%	0.38 [-0.00, 0.76]
Total (95%CI)			896			737	100.0%	-0.14 [-0.40, 0.12]

Heterogeneity: Tau^2 = 0.12; χ^2 = 48.61; df = 8 (P < 0.00001); I^2 = 84%
Test for overall effect: Z = 1.08 (P = 0.28)

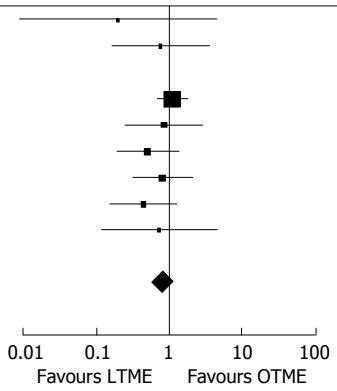


D

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	2	15	1.1%	0.20 [0.01, 4.57]
Baraga 2007	3	83	4	85	4.8%	0.76 [0.16, 3.50]
Gong 2012	0	67	0	71		Not estimable
Guillou 2005	72	253	34	128	49.0%	1.10 [0.68, 1.77]
Lujan 2009	5	101	6	103	7.5%	0.84 [0.25, 2.85]
Ng 2008	8	51	13	48	11.5%	0.50 [0.19, 1.34]
Ng 2009	9	76	11	77	12.5%	0.81 [0.31, 2.07]
Ng 2013	7	40	13	40	10.1%	0.44 [0.15, 1.26]
Zhou 2004	2	82	3	89	3.4%	0.72 [0.12, 4.40]
Total (95%CI)		766		656	100.0%	0.82 [0.59, 1.15]
Total events	106		86			

Heterogeneity: Tau^2 = 0.00; χ^2 = 4.57; df = 7 (P = 0.71); I^2 = 0%

Test for overall effect: Z = 1.16 (P = 0.24)

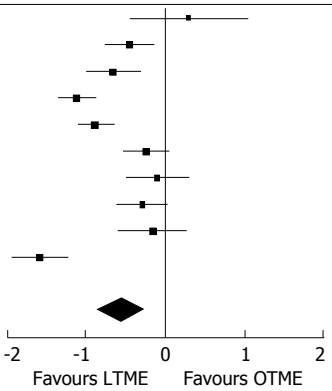


E

Study or subgroup	LTME Mean	LTME SD	LTME Total	OTME Mean	OTME SD	OTME Total	Weight	Std. Mean Difference IV, random, 95%CI
Araujo 2003	10.5	3.2	13	9.5	3.2	15	6.9%	0.30 [-0.44, 1.05]
Baraga 2007	10	4.9	83	13.6	10	85	10.5%	-0.45 [-0.76, -0.15]
Gong 2012	10.4	4.3	67	13.8	5.9	71	10.2%	-0.65, [-0.99, -0.31]
Guillou 2005	11	1.5	253	13	2.25	128	11.0%	-1.12 [-1.34, -0.89]
Kang 2010	8	1.25	170	9	1	170	11.0%	-0.88 [-1.10, -0.66]
Lujan 2009	8.2	7.3	101	9.9	6.8	103	10.7%	-0.24 [-0.52, 0.04]
Ng 2008	10.8	5.5	51	11.5	8.25	48	9.8%	-0.10 [-0.49, 0.29]
Ng 2009	8.4	5	76	10	6	77	10.4%	-0.29 [-0.61, 0.03]
Ng 2013	10.5	4.5	40	15	40.25	40	9.4%	-0.16 [-0.59, 0.28]
Zhou 2004	8.1	3.1	82	13.3	3.4	89	10.2%	-1.59 [-1.93, -1.24]
Total (95%CI)			936			826	100.0%	-0.55 [-0.86, -0.25]

Heterogeneity: Tau^2 = 0.21; χ^2 = 82.18; df = 9 (P < 0.00001); I^2 = 89%

Test for overall effect: Z = 3.53 (P = 0.0004)

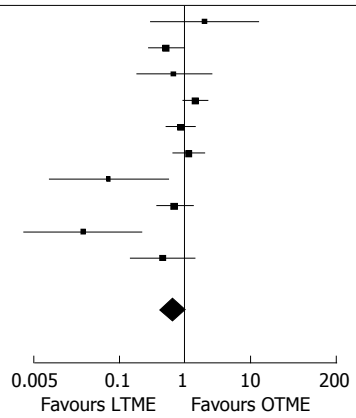


F

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	11	13	11	15	4.4%	2.00 [0.30, 13.26]
Baraga 2007	29	83	43	85	13.5%	0.52 [0.28, 0.98]
Gong 2012	4	67	6	71	7.3%	0.69 [0.19, 2.55]
Guillou 2005	150	253	64	128	15.6%	1.46 [0.95, 2.23]
Kang 2010	45	170	50	170	15.1%	0.86 [0.54, 1.39]
Lujan 2009	47	101	44	103	14.3%	1.17 [0.67, 2.03]
Ng 2008	39	51	47	48	3.8%	0.07 [0.01, 0.56]
Ng 2009	33	76	40	77	13.4%	0.71 [0.38, 1.34]
Ng 2013	21	40	39	40	3.8%	0.03 [0.00, 0.23]
Zhou 2004	5	82	11	89	8.8%	0.46 [0.15, 1.39]
Total (95%CI)		936		826	100.0%	0.69 [0.43, 1.08]
Total events	384		355			

Heterogeneity: Tau^2 = 0.30; χ^2 = 28.55; df = 9 (P = 0.0008); I^2 = 68%

Test for overall effect: Z = 1.62 (P = 0.11)

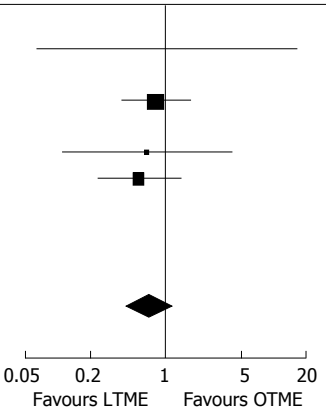


G

Study or subgroup	LTME Events	LTME Total	OTME Events	OTME Total	Weight	Odds ratio M-H, random, 95%CI
Araujo 2003	0	13	0	15		Not estimable
Baraga 2007	1	83	1	85	3.5%	1.02 [0.06, 16.65]
Gong 2012	0	67	0	71		Not estimable
Guillou 2005	21	253	13	128	52.2%	0.80 [0.39, 1.66]
Kang 2010	0	170	0	170		Not estimable
Lujan 2009	2	101	3	103	8.4%	0.67 [0.11, 4.12]
Ng 2008	12	51	17	48	35.9%	0.56 [0.23, 1.35]
Ng 2009	0	76	0	77		Not estimable
Ng 2013	0	40	0	40		Not estimable
Zhou 2004	0	82	0	89		Not estimable
Total (95%CI)		936		826	100.0%	0.70 [0.41, 1.18]
Total events	36		34			

Heterogeneity: Tau^2 = 0.00; χ^2 = 0.45; df = 3 (P = 0.93); I^2 = 0%

Test for overall effect: Z = 1.33 (P = 0.18)



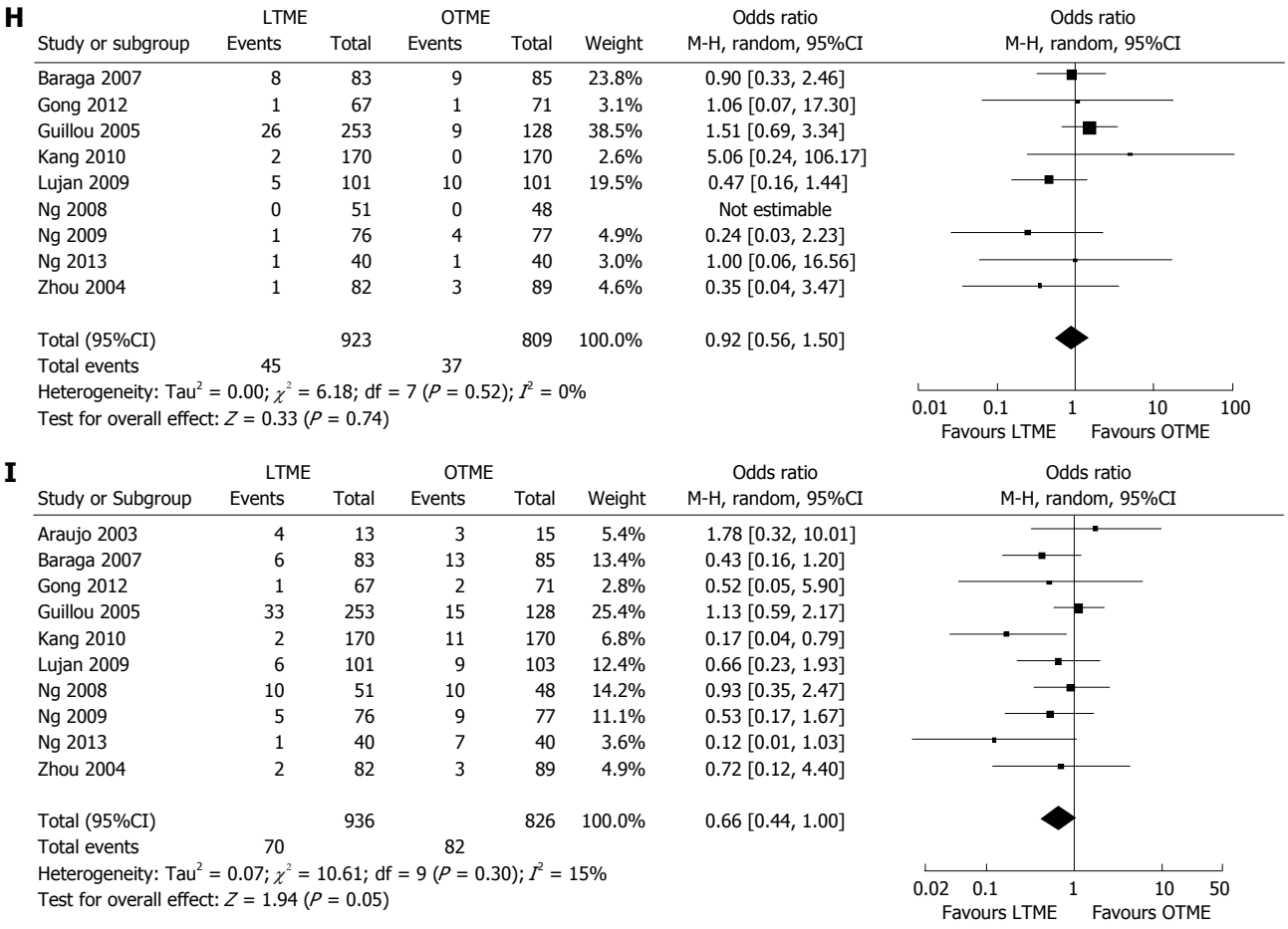


Figure 3 Forest plot. A: Of risk of incomplete total mesorectal excision following laparoscopic total mesorectal excision (LTME) *vs* open total mesorectal excision (OTME) for rectal cancer. Odds ratios are shown with 95%CIs; B: Of risk of risk of circumferential resection margin positivity following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; C: Of number of harvested lymph nodes following LTME *vs* OTME for rectal cancer. Standardized mean differences are shown with 95%CIs; D: Of recurrence following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; E: Of length of stay following LTME *vs* OTME for rectal cancer. Standardized mean differences are shown with 95%CIs; F: Of complications following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; G: Of all-cause mortality following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; H: Of anastomosis leak following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs; I: Of surgical site infection following LTME *vs* OTME for rectal cancer. Odds ratios are shown with 95%CIs.

patients of rectal cancer, there is a higher risk of surgical site infection, higher risk of incomplete total mesorectal resection and prolonged length of hospital stay following OTME compared to LTME. The oncological outcomes like the number of harvested lymph nodes, incidence of tumour recurrence and risk of positive resection margins were statistically similar in both groups. In addition, the clinical outcomes such as operative complications, anastomotic leak and all-cause mortality were comparable between both approaches of the mesorectal excision. LTME appears to have clinically and oncologically measurable advantages over OTME in patients with primary resectable rectal cancer in both short term and long term follow ups.

The findings of this article are consistent with previously published Cochrane review and a meta-analysis[43,44]. Majority of the studies in the Cochrane review[44] were non-randomized, trials and therefore the conclusion was considered weaker and biased. Similarly a recently published meta-analysis[43] failed to demonstrate the oncological safety and advantages of LTME over OTME. This review article presents a comprehensive assessment on the oncological safety of the LTME in addition to the proven clinical advantages of laparoscopy in the curative resections of rectal cancer. Proven clinical advantages of LTME have also been reported in in many published studies[32,33,35,42] which include the lesser blood loss, shorter length of hospital stay and lower postoperative pain score. In addition, the oncological adequacy of LTME has been confirmed in many recent publications[34,37,38,40].

Authors are fully aware of the fact that there are several limitations to this study. There is significant heterogeneity among included studies. Causes of heterogeneity are both clinical as well as methodological in terms of trial recruitment process. Included studies recruited patients with different stages of the rectal cancer and therefore one would expect their oncological outcome different. Combined analysis of studies on rectal cancer patients with and without neoadjuvant treatment can potentially influence the oncological outcomes which would result in biased conclusions. Variable grade and stage of the disease in recruited patients can also manipulate overall

survival and risk of recurrence. Preoperative nodal disease staging by MRI scan is a standard approach and all included studies did report the use of this imaging prior to surgery. Preoperative diagnostic and staging modalities across the included trials were significantly heterogeneous and therefore can potentially be a strong source of study sample contamination leading to biased outcomes. Colorectal follow up protocol among various centres conducting these trials was significantly diverse and inconsistent. Future trials should be directed towards the involvement of major colorectal units recruiting patients of similar stage and grade of the disease with different arms evaluating outcomes with and without neoadjuvant chemoradiotherapy. In addition, an agreed preoperative staging as well follow up protocol will also help to curtail the clinical and methodological flaws reported in previous trials.

COMMENTS

Background

Total mesorectal excision (TME) has been the gold standard treatment for the management of rectal cancer. Laparoscopic approach for TME has been reported with several advantages such as quicker recovery, reduced postoperative pain and shorter hospital stay. But the limitations compared to open approach include higher cost, longer learning curve and longer operating time.

Research frontiers

Due to clinically measureable advantages, the laparoscopic approach may be a preferred way forward as long as oncological safety of both approaches is at least similar. Several non-randomized and randomized studies have reported the inconsistent oncological findings following laparoscopic TME and precise guidelines are still scarce. Since the introduction of new generation of laparoscopic instruments and stapling devices, the recently published studies have reported encouraging results in favour of laparoscopic TME.

Innovations and breakthroughs

This article highlights the role of laparoscopic approach for TME in current situations. This article reports the oncological safety of laparoscopic TME in terms of clear circumferential resection margins, number of harvested lymph nodes, recurrence and mortality following both open and laparoscopic TME. This article compared to other peer review publications on the same subject provides the latest and strongest evidence and may assist the colorectal surgeons in decision making.

Peer review

It is an important topic, clear presentation, good readability, appropriate methods, precise results, interesting discussion, coherent tables, unambiguous conclusion. This is a very good paper.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

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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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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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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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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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

Patent (list all authors)

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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