Review Article

Enhanced recovery for gynecological oncology surgery—review

Ian Davis, Chris Jones

Department of Anaesthetics, Royal Surrey County Hospital, Guildford, Surrey, UK

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Correspondence to: Dr. Ian Davis. Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group (SPACeR), Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK. Email: Ian.davis5@nhs.net.

Abstract: Enhanced recovery after surgery (ERAS) programs initially developed for colorectal surgery two decades ago have revolutionized the management of the surgical patient. By recognizing that the whole peri-operative period, not just the surgery itself, provides opportunities for evidence-based morbidity and length of stay (LoS) reducing interventions to be made, the quality and cost effectiveness of patient care has been improved. By considering and optimising the patients' pre-operative physical (prehabilitation, carbohydrate loading, avoidance of bowel prep) and psychological (pre-admission education and counselling) condition, they arrive for surgery at a significant advantage. Intra-operatively, using an appropriate balanced anaesthetic technique, combined with minimally invasive surgery where possible, sensible fluid management, and multimodal analgesia continuing into the post-operative period, functional recovery has been shown to be enhanced. The promotion of early ambulation is facilitated by good multimodal analgesia, and reduced usage or earlier removal of abdominal drains and urinary catheters, which in turn reduces the venous thromboembolism (VTE) and post-operative infection risk. Robust discharge pathways including education of patients on discharge, may help to minimise unplanned readmissions. The ERAS principles applied to gynecological oncology surgery have been shown to be effective however the evidence is evolving and hence it is essential the adherence to and effectiveness of these pathways is continually audited.

Keywords: Enhanced recovery after surgery (ERAS); gynecologic oncology surgery; perioperative care

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Introduction

Enhanced recovery after surgery (ERAS) initially developed by European surgeons around the mid 1990's culminating in the formation of the ERAS study group in 2001, has transformed, and is continuing to transform the peri-operative management of the surgical patient.

The group demonstrated that the whole peri-operative period, from pre-admission to post-operative recovery, not just the surgery itself, had a large influence on outcome. (1)

By applying evidence based interventions focused on ensuring the patient undergoes surgery optimised from both a psychological and physiological viewpoint, and by continuing to minimise the stress response to surgery in the peri and post-operative periods, it has been repeatedly demonstrated that length of stay (LoS), post-operative complications, and cost have been significantly reduced (2-4).

Initial guidelines were published by the ERAS society for colorectal surgery in 2005. This was soon followed by guidelines for other surgical specialties, with the first major gynaecology/oncology guidelines published in 2016 (5). An update to these guidelines has been published in 2019 (6).

In this review article, an overview of the major gynecological cancers and their incidence is described, followed by a description of the major features of enhanced recovery in gynecological oncology surgery and the changes from the previous guidelines. Also, emerging evidence that may further improve patient care and influence future

Table 1 Incidence, 5-year survival and mortality of gynecological cancers in the UK

Cancer	Incidence[a] per 100,000 [2016]	5-year[b] survival %	Mortality[a] per 100,000 [2016]
Ovarian	12.2	46	6.6
Uterine	15.6	79	3.8
Cervix	5.0	67	1.4
Vulval	2.1	64	0.8
Vaginal	0.4	64	0.2

Adapted from Cancer Research UK website, data reproduced with permission https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type, accessed September 2019. [a], age-standardized rates; [b], predicted age-standardised net 5-year survival.

guidelines will be reviewed.

Gynecologic cancers—an overview

The 5 main gynecological cancers comprise uterine (endometrial & uterine sarcoma), ovarian, cervical, vulval and vaginal. For this review we will be considering endometrial, ovarian and cervical only. For UK epidemiological data see *Table 1*.

Cervical cancer

Cervical cancer is the 4th most common cancer worldwide, and the most common genital tract cancer in women of less developed countries (7). The culprit is human papilloma virus infection (HPV), and these cases would be largely preventable with an adequate HPV vaccination & screening programme. The predominance of cases are squamous cell carcinoma, with spread of tumour occurring via the vaginal mucosa, to the myometrium and then the paracervical lymphatic system. Spread can also occur via the obturator fascia to other pelvic viscera such as the rectum and bladder. Haematogenous spread is typically to the lung, liver and bone. Patients with early disease may only require a simple hysterectomy, however more advanced disease may require removal of part of the vagina, parametrium, uterosacral ligament and uterovesical fold, and pelvic node dissection (8).

Ovarian cancer

Patients with ovarian cancer often present late with advanced disease. It is therefore the gynecological cancer associated with the lowest survival rate. Ovarian cancer differs from haematogenously metastasizing tumours as spread is primarily within the peritoneal cavity and is only superficially invasive. The rapidity of the proliferation to involve visceral organs and the temporary sensitivity to chemotherapy contributes to the low survival rate. Spread can continue via surfaces of the peritoneal cavity to the paracolic gutters, hemidiaphragm, and intestinal mesentery. Haematogenous spread can occur resulting in lung and bone metastases, pericardial effusions and central nervous system involvement. Due to the nature of the disease surgical staging is required.

Endometrial cancer

Endometrial cancer is the most common genital tract malignancy in the developed world (8). It is a hormone dependent cancer with the most significant risk factors being; unopposed oestrogen, sedentary lifestyle and obesity (9).

Spread can occur locally, via the fallopian tubes (giving rise to peritoneal metastases), lymphatics, and/or haematogenously resulting in metastases to the lung, liver, bone, and brain. Treatment is via total hysterectomy, bilateral salpingo-oophorectomy, and full pelvic lymphadenectomy.

Major features of gynecologic oncology surgery enhanced recovery

Pre-operative

Pre-admission education and counselling

As the title implies supplying the patients with information and psychological counselling on what to expect from the pre-operative phase through to day of surgery and onto the recovery phase. Reduced stress levels could have a positive effect on limiting catabolic hormones in the peri operative

period resulting in reduced morbidity, faster recovery and reduced LoS. A 2014 small study looking at pre-operative psychological health education pre hysterectomy demonstrated a reduction in day of surgery anxiety and depressive symptoms and serum cortisol compared to control (10).

Anxiety is a known risk factor for poorly controlled post-operative pain which could in turn lead to increased post-operative stress response and its associated sequelae, increased post-operative stress hormone levels, delay in bowel function and delay in mobilising for example. A single centre randomised control trial (RCT, n=74) demonstrated a reduction in post op pain and nausea scores and a higher wellbeing score in those receiving pre-operative education in elective open cholecystectomy as part of an ERAS pathway (11). A Cochrane review from 2016 reviewed the effects of psychological preparation on post-operative pain, behavioural recovery, negative affect and LoS. The authors concluded the evidence wasn't strong enough to reach a firm conclusion of benefit (12), but noted the intervention was unlikely to be harmful.

In summary although robust evidence demonstrating the benefits of patient education and counselling specific to major gynaecological oncology surgery is lacking, it is unlikely to cause harm and most likely is beneficial, and this is reflected by an increase in the strength of recommendation by the authors of the most recent ERAS gynaecologic oncology guidelines (6).

Prehabilitation

By considering the patient holistically, prehabilitation aims to pre-emptively prepare the patient for the impending physiological and psychological insult of cancer treatment and surgery. It has been defined as "*a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment*, *includes physical and psychological assessments that establish a baseline functional level*, *identifies impairments*, *and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments*" (13).

A commonly described regime (6) would consist of:

(I) Aerobic and resistance exercises to improve physical function, body composition, and cardiorespiratory fitness;
(II) Targeted functional exercises to minimize/prevent impairments;
(III) Dietary interventions to support exercise-induced anabolism as well as mitigate disease and/or treatment-related malnutrition;
(IV) Psychological interventions to reduce stress, support behaviour change, and encourage overall well-being.

Consider as an example a cachectic smoker who is very anxious pre major cancer surgery. From a physiological and psychological viewpoint, they are not well prepared to deal with the insult to come. Malnutrition and minimal reserve of muscle mass to attenuate the catabolic effects of cancer treatment and surgery, result in further impairment of the respiratory function post op and impaired ability to mobilise, impaired immune function and wound healing, and hence increasing risk of developing post-operative infections and generalised failure to thrive. Due to impaired cardiorespiratory fitness the oxygen delivery may be inadequate to meet the metabolic requirements for wound healing and recovery from major surgery. The anxiety and depression component may cause the patient fail to comply with smoking cessation pre-operatively, again contributing to impaired oxygen delivery and wound healing. Post-operative depression could negatively affect appetite affecting wound healing and contributing to the catabolic state as well as compliance with other interventions such as physiotherapy.

At the other end of the spectrum a young and highly motivated previously physically fit patient with no pre-existing medical or mental health problems. They may likely still benefit from the above interventions, however the emphasis on prehabilitation may differ from first scenario described. A meta-analysis examining the effects of exercise based prehabilitation in an intrabdominal surgical population (14) found a reduction in post-operative all cause and pulmonary complications, however the authors felt there was insufficient evidence to comment on the effect on LoS and mortality. A subsequent meta-analysis looking at the benefits of nutritional prehabilitation (with and without exercise component) in a colorectal surgical population (15) found that LoS was significantly reduced. The authors commented that stratification of outcomes by nutritional status and functional capacity might demonstrate clearer results and provide data to assist with risk stratification. Both studies' authors commented on the small number of included studies and the heterogeneity of methodology limiting their ability to draw firm conclusions from the available data.

In summary multimodal prehabilitation is likely beneficial however it may be that tailoring regimens to the patient's pre-operative nutritional and functional status

may be appropriate, especially with regard to exercise interventions, "one size does not fit all" (13).

Pre-operative bowel preparation

Pre-operative mechanical bowel preparation (MBP) has been practiced for more than a century. It was believed that the presence of unprepped bowel would increase anastomotic leak and infection rates. This assumption was based on expert opinion and not scientific studies (16). Even under laparoscopic conditions, where no bowel resection is planned, it was believed that MBP would improve surgical conditions in terms of ease of bowel handling and view of surgical field. Again, there is no evidence to support this neither in gastrointestinal nor in minimally invasive gynaecological surgery where no colonic resection/ anastomoses are planned (6).

Recently several studies have seen a resurgence of bowel prep in the colorectal surgical population in the guise of oral antibiotics and MBP. Of note a retrospective analysis of 32,359 patients from the American College of Surgeons National Surgery Quality Improvement Program database showed a reduction in any surgical site infection (SSI), anastomotic leak, ileus and LoS with oral antibiotics & MBP, and oral anti biotics only, but no benefit from MBP alone.

It is therefore sensible that current ERAS guidelines do not recommend routine use of bowel prep. Surgical discretion is only acceptable in cases involving colonic resection, and in these cases MBP should be combined with oral antibiotics, or oral antibiotics used alone (6).

Pre-operative fasting & carbohydrate treatment

The traditional practice of fasting prior to surgery causes the body's metabolism to adopt the fasted state, with a marked reduction in anabolic hormones, relative to catabolic hormones. Trauma in the form of elective surgery also causes a release of catabolic hormones that promote release of glucose from the liver, fatty acid production, release of amino acids from skeletal muscle tissue, and insulin resistance. There is evidence that by loading patients with carbohydrate pre surgery, post-operative insulin resistance can be reduced (17,18), and post-operative protein synthesis increased (19). A Cochrane review (20) of studies comparing pre-op carbohydrate treatment to placebo or fasting in elective (non-gynaecological) surgery demonstrated a modest reduction in LoS, with no increase or decrease in post-operative complication rates. In 2 of the 19 studies reviewed pre-operative carbohydrate treatment reduced time to flatus and in 3 of the 19 studies it increased post-operative insulin sensitivity. There was no evidence of any increased complications, with no reports of aspiration pneumonitis.

Venous thromboembolism (VTE) prophylaxis

In patients with cancer VTE is the second leading cause of death. It is well known that patients with active malignancy are at higher risk of VTE than the non-cancer population with a 4–7 times increased risk (21). However the risk differs between malignancies, with gynecological malignancy considered in the high risk bracket. Of the gynecological malignancies, VTE incidence is 3–4% for cervical, 7–9% for endometrial, and highest in ovarian cancer at 17–38% (6). Even in ambulatory patients the VTE risk is significant and continues well beyond the post-operative phase. In those undergoing neoadjuvant chemotherapy for ovarian cancer, a quarter developed VTE's, of which half occurred prior to surgery during chemotherapy cycles (22).

Pre-operative initiation of anticoagulant chemoprophylaxis has been shown to significantly reduce the risk of VTE in a large retrospective study of surgical oncology patients (23) and also in a cohort study (n=527) (24) of complex gynecological surgery patients (when added to standard care of pre op sequential compression devices, and combined with extended post op prophylaxis in those at highest risk.) Both studies commented that there was no increase in significant bleeding.

Combining pharmacological prophylaxis with pneumatic compression devices achieved the greatest reduction in VTE rates in a gynaecology oncology population, and graduated compression stockings when fitted properly add further benefit especially if combined with any other method of VTE prophylaxis (6).

The American College of chest physicians guidelines state that in those at high risk of VTE undergoing major abdominopelvic surgery for cancer, pharmacological prophylaxis in the form of LMWH or unfractionated heparin should be continued for 28 days, in addition to use of mechanical prophylaxis, however balancing risk of developing VTE with risk of bleeding, and delaying use of pharmacological prophylaxis until the bleeding risk has diminished (25).

SSI reduction bundles

The following components may not individually significantly reduce SSIs defined as infections in the surgical incision or organ space within 30 days of surgery, however

in varying combinations they have been shown to be effective (26,27).

Pre-op washing with chlorhexidine

There is evidence that pre-operative bathing/showering with chlorhexidine as part of an infection reduction bundle has reduced incidence of cellulitis after abdominal hysterectomy (28).

Antimicrobial prophylaxis

The use of a first-generation cephalosporin is recommended to cover skin flora for simple procedures such as hysterectomy. An alternative regimen may be required in those with a genuine beta lactam allergy. Additional cover is needed when the bowel is entered. In addition, if the patient is MRSA positive a glycopeptide antibiotic may be required. The dose may need to be adjusted to body weight, and care must be taken in the obese as with some antibiotics such as gentamicin using the actual body weight may not be appropriate. Most institutions have an antibiotic guidance protocol to assist in dose calculations. If the surgery is of long duration, for the 1st & 2nd generation cephalosporins cefazoline and cefuroxime, redosing should occur at 4 hours. Also, if blood loss exceeds 1.5 litres then redosing should occur (29).

Skin disinfection

Chlorhexidine-alcohol has been shown to reduce the SSI rate by 41% more than povidone-iodine (30).

Prevention of hypothermia

Multiple studies have shown an association with peri operative hypothermia and increased risk of SSI's (31,32). However a recent meta-analysis (33) and large cross sectional study did not demonstrate this association (34), hypothermia was associated with other adverse outcomes such as increased ICU admissions and increased LoS (34). Hence peri operative normothermia should be the goal with avoidance of hypo and hyperthermia.

Surgical drains & nasogastric tubes

Surgical drains can provide an entry point for pathogens favouring the development of SSIs, they also hinder mobilisation. A large prospective observational double centre study (n=5,175) found an increase in SSIs with surgical drain usage, and the authors recommended against their routine use except for in specific situations such as longer procedures and clean orthopaedic trauma surgery (35). Nasogastric tubes may increase the risk of post-operative lower respiratory tract infection without reducing the risk of post-operative surgical complications (36). Therefore in gynaecology oncological surgery the routine use should be avoided, however if the surgeon cognisant of the lack of robust evidence for their routine use, feels that in a select case the benefits outweigh the risks then their use may be indicated.

Peri-operative glucose control

With the increasing incidence of diabetes in the developed world and significant evidence implementing hyperglycaemia as a risk factor for developing SSIs, avoiding peri-operative hyperglycaemia is essential. However what blood glucose range should be targeted?

A renowned study from 2001 comparing tight *vs.* more liberal glycaemic control (in predominantly post-operative surgical patients requiring critical care) showed a 1/3rd reduction in mortality (37). However a subsequent larger study attempting to maintain a similar tight glycaemic control found both a significant increase in incidence of hypoglycaemic episodes, and an increased mortality in the tight glycaemic control group (38).

Average peri operative blood glucose appears related to 30-day mortality in a linear fashion in non-cardiac surgical patients (39). Currently the American Diabetes Association, the Joint British Diabetes Societies, and the Society of Thoracic Surgeons recommend initiating insulin treatment for peri-operative blood glucose >10 mm/L (40). Peri-operative glycaemic control may be more important than pre op HbA1c in predicting 30-day mortality (39). Patients should be screened for diabetes pre operatively and extremes of blood sugar should be avoided in the peri operative period.

Peri-operative—anaesthetic & surgical technique, fluid management, analgesia

The anaesthetic technique will vary depending on the magnitude of the operation, with different techniques being employed for open *vs.* laparoscopic *vs.* robot assisted surgeries. However the basic principles should remain the same, and are aimed at, minimising the stress response to surgery and disturbances in physiology, maintaining euvolemia, minimising opiate consumption in the peri operative period, and enhancing recovery.

(I) Use of short acting anaesthetic agents, sevoflurane or desflurane if volatile anaesthesia, propofol and remifentanil target-controlled infusions if total intravenous anaesthesia (TIVA) is appropriate;

(II) Monitoring of anaesthetic depth in certain cases, i.e., elderly and major surgery (mandatory with TIVA);

(III) Use of multimodal analgesia to minimise opiate use. For example, intravenous acetaminophen,

nonsteroidal anti-inflammatory drugs (NSAIDS) where tolerated, analgesic adjuncts, i.e., magnesium, tramadol, local anaesthetic infiltration to port sites;

(IV) The omission of nitrous oxide and the administration of at least two anti-emetic drugs;

(V) Use of regional techniques where appropriate, epidural or sub arachnoid blocks, or intra fascial plane blocks/wound catheters with the aim of minimising opiate use post operatively;

(VI) Intra operative fluid management; tailored to the specific patient and operation, may involve the use of cardiac output monitoring;

(VII) Intra operative ventilation aiming for 6–8 mL/kg ideal bodyweight, with adequate PEEP;

(VIII) Monitoring and full reversal of neuromuscular blockade.

A simple laparoscopic hysterectomy in a patient with no risk factors for chronic pain may not require any neuraxial or regional blockade, with a multimodal analgesic approach consisting of local anaesthesia infiltrated to the port sites, paracetamol, NSAID's intra and post op (if tolerated), minimising opiate requirements. Adjunctive analgesics e.g. tramadol may be added as required.

A more extensive procedure, for example a robotic assisted hysterectomy, bilateral salpingo-oophorectomy and complex pelvic node dissection may benefit from sub arachnoid anaesthesia. In our institution we use high dose intrathecal diamorphine, with low dose local anaesthetic, and where possible TIVA with propofol and remifentanil target-controlled infusions.

Finally at the other end of the spectrum, a laparotomy for ovarian cancer involving extensive debulking with the incision extending supra umbilically to enable para aortic node dissection, at our institution would receive a thoracic epidural, again where possible with a total intravenous anaesthetic technique, and post-operative high dependency care and conversion to multimodal oral analgesia at the earliest possibility.

TIVA

A 2019 meta-analysis (41) looking at 7,866 patients who underwent surgery for breast, oesophageal and non-small cell lung cancer, has suggested that propofol TIVA may confer improved recurrence free survival and overall survival especially in the major surgical cases. The authors conceded that due to the major limitations in the studies in the meta-analysis, prospective randomised trials are required to guide practice.

Even though the evidence is not strong enough to necessitate a change in practice, we have noticed an increasing trend in propofol TIVA usage in our institution especially for major cancer surgery.

Bispectral index (BIS) guided depth of anaesthesia monitoring

There is currently some uncertainty as to whether BIS guided depth of anaesthesia monitoring during volatile based general anaesthesia is beneficial. When used in conjunction with traditional markers for assessing depth of anaesthesia BIS can help reduce the likelihood of awareness and also improve post-operative recovery by preventing excessively deep anaesthesia (42,43). This may lead to a reduction in post-operative delirium and cognitive dysfunction especially in the >60 age group (43).

A recently published study (ENGAGES) (44) did not correlate burst suppression (used synonymously as a marker of excessively deep levels of anaesthesia) with increased post-operative delirium and cognitive dysfunction. Interestingly the control group had a higher 30-day mortality. Further analysis of the ENGAGES results suggested that the degree of EEG suppression in the study group may have been too great to be able to distinguish any difference with regards to the primary outcome between the two groups. Furthermore, it appears that the median time in EEG suppression was substantially greater in those experiencing delirium than those not (45).

Several other large studies' results are imminent at time of writing and these may eventually further influence practice regarding the use of BIS for optimising anaesthetic depth. Our current practice is to use BIS guided depth of anaesthesia monitoring for all TIVA cases and high-risk patients or major surgical cases of anticipated prolonged duration.

Peri-operative analgesia

Neuraxial/regional anaesthesia

(I) Thoracic epidural anaesthesia (TEA)

For complex open surgery TEA has traditionally been shown to provide superior pain relief (46) with decreased VTE, pulmonary and respiratory complications (47) compared to systemic analgesia. It may also reduce the amount of intra-operative anaesthetic agent and opiate required which may benefit post-operative recovery. It is still currently one of the recommended analgesic components for open surgery by the American Society of

Colon & Rectal Surgeons (48). However there is conflicting evidence as to the benefit of epidural analgesia versus other modalities, for example fascial plane blocks. A small study in the colorectal population focusing on non-analgesic factors such as time to first flatus and LoS, demonstrated reduced LoS in the fascial plane block group (49). The evidence directly comparing thoracic epidural with fascial plane blocks or local anaesthetic wound catheters is insufficient to guide on optimum technique. It is reassuring that if TEA placement is not possible or fails, that reasonable alternatives exist, and as further evidence emerges it may be apparent that non epidural local anaesthetic techniques as part of a multimodal analgesic strategy may even be superior for enhanced recovery.

(II) Intrathecal opiates

For laparoscopic, robotic assisted, and some open surgeries, a low dose of local anaesthetic in combination with moderate to long acting opiate such as morphine prior to general anaesthesia has been employed successfully. Two recent studies comparing intrathecal morphine (ITM) *vs.* epidural anaesthesia for patients undergoing midline laparotomy for gynaecological malignancy (50) and laparotomy for abdominal hysterectomy (51) have reported pain scores to be either equivalent or less in the ITM group, with reduced total opiate requirements and reduced LoS (50).

(III) Transversus abdominis plane block

As described earlier transversus abdominis plane block using liposomal bupivacaine has been shown to reduce LoS in a small study in colorectal patients (49). A meta-analysis of this block being used for abdominal surgery showed reduced pain scores and opiate consumption post operatively, however the analgesic efficacy was felt to be inferior to ITM (52). A subsequent meta-analysis reviewing the efficacy of TAP blocks compared to no/sham block in both open and laparoscopic/robotic hysterectomy found that it reduced post-operative analgesic requirements especially in abdominal hysterectomy, but was not as effective in laparoscopic or robotic hysterectomy (53).

(IV) Local anaesthetic infiltration & wound catheters

Local anaesthetic infiltration to port sites has been shown to be as effective as TAP blocks in an RCT of laparoscopic gynaecological surgery (54). Surgical site infiltration with liposomal bupivacaine has been shown to be more effective than bilateral TAP blocks with plain bupivacaine in terms of pain relief at rest and on coughing, and reduced opiate consumption up to 48 h after abdominal hysterectomy (55). In studies comparing continuous infiltration of local anaesthetic via wound catheters to epidural analgesia in open nephrectomy, open gastrectomy and open hepatobiliary surgery, analgesia in the wound catheter group was satisfactory and non-inferior to epidural analgesic efficacy (56-58).

Analgesic adjuncts

(I) Lignocaine infusion

The evidence for intraoperative lignocaine infusion is unclear. A Cochrane review in 2015 suggested there may be some benefit with regards to reduced post-operative pain, PONV and time to return of bowel function (59). However an update to this meta-analysis (60) stated that the evidence was not adequate to support its use. The poor quality and heterogeneity of the studies with regards to dose of lignocaine used, infusion rates, infusion duration, may have contributed to any benefits not being demonstrated in the most recent update. Chronic post-surgical pain is another area in which peri operative lignocaine infusions may be of benefit, but again the authors of the systematic review (61) commented on the limitations of the studies, and the need for further research in this area. There are currently multiple studies ongoing looking at peri-operative lignocaine infusions the results of which are anticipated.

(II) Magnesium

An antagonist at the NMDA receptor, magnesium given as a bolus and/or an infusion has been shown to reduce post-operative opiate requirements and pain scores without any serious side effects (62). We use a magnesium infusion as part of a multimodal analgesic strategy. Care must be taken in ensuring adequate reversal of neuromuscular block due to the potentiating effects of magnesium on non-depolarising neuromuscular blocking agents.

(III) Ketamine

Via reversible blockade of the NMDA receptor, as well as actions on but not limited to the monoaminergic, gamma-aminobutyric acid (GABA) and opioid receptors, its use in sub anaesthetic doses reduces post-operative pain intensity and analgesic consumption. It can be given as an intraoperative bolus or infusion, or a post-operative bolus if opiate analgesia is inadequate (63). The optimal dose and timing are unclear.

(IV) Dexamethasone

A meta-analysis showed that a single peri-operative dose resulted in a small but statistically significant reduction in post-operative pain and opioid consumption possibly related to its anti-inflammatory properties (64).

Peri-operative fluid management

The consequences of inadequate and excessive intra-

operative fluid administration have been well described in the literature. In normal conditions the renal cortex receives 90% of the blood flow to the kidney, and hence the renal medulla is vulnerable to reductions in renal blood flow. A decrease of 40–50% can trigger ATN (65). In addition to AKI, other described complications of hypovolaemia include SSIs, sepsis, and increased LoS.

Excessive fluid administration has traditionally been cited as contributing to impairing cardiopulmonary, and gastro-intestinal function, and increasing post-operative complications (66) and LoS (67). A large population based study also found that the hospitals with highest peri-operative fluid balances had significantly longer LoS (68).

In recent years peri operative fluid management has improved and trended towards becoming restrictive, possibly too restrictive. This may explain the findings of a more recent multicentre trial (69) comparing restrictive to liberal fluid administration in the intra and immediate post-operative period (up to 24 hours). This study found the liberal group had a lower incidence of acute kidney injury and SSIs, with no significant differences in mortality or other outcomes.

The evolution in the literature regarding peri operative fluid management emphasises the need to maintain euvolemia, and in high risk and major surgical cases, goal directed fluid therapy is one of the tools available that can help achieve this aim. By assessing fluid responsiveness via changes in stroke volume in response to a fluid bolus, or by assessing the variation in stroke volume with the respiratory cycle, the volume status of the patient may be more accurately estimated. This technique has been successfully demonstrated in a recent large study that compared goal directed fluid therapy *vs.* conventional therapy. There was reduced incidence of post-operative complications, and reduced LoS in the goal directed group (70). This correlated with an earlier systematic review also demonstrating reduced post-operative complications when GDFT was used (71). However benefit was not shown in a more recent meta-analysis and it may be that the general improvement in fluid management and care due to ERAS pathways has made it harder to detect a difference (72). Goal directed fluid therapy may be still be a useful tool when used in conjunction with the other clinical indices in helping the clinician achieve and maintain euvolaemia.

Surgical technique

Minimising the stress response to surgery is one of the main principles of enhanced recovery. Minimally invasive surgery, laparoscopic or robotic assisted, has led to improved patient outcomes in terms of blood loss, analgesic requirements, return of bowel function, LoS and return to normal daily activities (6). The benefits may be due to a reduction in tissue trauma and hence the associated endocrine and metabolic changes which can stress the patient's reserves and immune function. A study comparing the stress hormone levels at 24 hours post major vascular surgery showed significantly reduced levels in the laparoscopic group (73). A meta-analysis of 71 studies assessing cortisol levels in the peri operative period showed that minimally invasive procedures did not demonstrate a peri operative cortisol peak, whereas more invasive surgeries caused a cortisol surge that was more pronounced in older subjects, women and patients undergoing open surgery and general anaesthesia, with higher levels persisting into the post-operative period (74).

Most of the data demonstrating the benefits of ERAS in gynecologic oncology surgery are in open surgery. However, there is evidence that implementation of ERAS in minimally invasive gynecologic surgery is beneficial and due to the improved surgical recovery, minimally invasive surgery is preferred for appropriate patients (providing long term oncological outcomes are not affected) (6).

Post-operative management

Multi modal analgesia

The goal of the intra operative use of multimodal anaesthesia and analgesia is not only to minimise the stress response to surgery, but also to reduce the amount of anaesthetic agent and opioid required, thereby facilitating prompt return of full cognitive function post operatively. By minimising opioid use, a reduction in opioid related side effects such as sedation and respiratory depression, nausea, urinary retention and delayed return of bowel function can be achieved. The multimodal philosophy must continue into the post-operative phase with the goal of expediting the recovery of patients to their pre-operative condition. Thoracic epidurals despite often providing excellent analgesia can delay enhanced recovery by several mechanisms. (I) Delaying ambulation possibly as a result of a dense block or postural hypotension, restriction from the epidural catheter/pump, or inadequate analgesia around the time of catheter removal. (II) Delay in transitioning to full multimodal oral analgesia hence hindering forwards progress in the recovery pathway.

The use of analgesics targeting different sites of the

pain pathway, for example acetaminophen, NSAID's (cyclo-oxygenase inhibition), local anaesthetic infiltrating catheters (neuronal sodium channel blockade), tramadol (mu receptor agonism and serotonin and noradrenalin reuptake inhibition) collaborate to reduce the amount of post-operative opioid required.

Prevention of post-operative ileus

Often a cause of delay in discharge, promoting early return of bowel function is major enhanced recovery goal. Rates are high in gynecologic oncology surgery especially after debulking surgery for ovarian cancer. Performing minimally invasive surgery, avoidance of fluid overload, minimisation of opioid drugs via a multimodal technique, early feeding and mobilisation have been shown significantly reduce the rates of post-operative ileus as part of an ERAS bundle (6). In patients undergoing planned bowel resection, the peripherally acting mu receptor antagonist alvimopan, given pre and post operatively, has been shown to reduce time to bowel recovery and reduce the incidence of post-operative ileus in multiple surgical specialties including gynaecologic oncologic surgery (75,76). Currently it is only approved by the FDA for patients undergoing planned bowel resection.

Nutrition

Early feeding is a key principle of enhanced recovery. An adequate nutritional state is vital to facilitate the repair of tissues damaged during surgery. It was previously believed that early feeding could result in complications such as vomiting and aspiration, anastomotic break down, and wound dehiscence. However this assumption wasn't evidence based. A recent meta-analysis comparing the effects of early versus delayed oral fluids and food in major benign and malignant gynaecological surgery (77) demonstrated benefits in terms of faster return of bowel function, fewer infectious complications, shorter LoS and increased patient satisfaction with no increase in other complications. In the GI surgical population meta analyses report that feeding <24 hours post-surgery is associated with reduced morbidity (78) and mortality (79).

Recent guidelines recommend 2 g of protein/kg/day and 25–30 kcal/kg/day, to attenuate the catabolic effects of surgery and to promote anabolic processes required for recovery. In patients achieving <50% of nutritional goals orally, enteral feeding should be considered. In some patients who cannot meet their nutritional needs enterally, parenteral nutrition may be needed. Protein delivery appears to be more important than total calorie delivery (80).

Drains, nasogastric tubes & urinary catheters

The routine use of abdominal and vaginal drains and nasogastric tubes reduces post op mobility, and increases associated infections (81). A Cochrane review did not find retroperitoneal drain placement beneficial post pelvic lymphadenectomy (82). The evidence for early removal of urinary catheters is not as large as in other surgical specialties, however there is evidence to suggest that early removal results in shorter LoS in surgery in both malignant and benign gynaecology surgery (83,84) and reduced incidence of urinary tract infection post total abdominal hysterectomy (84). Patients who have undergone pelvic surgery are at risk of voiding problems and post voiding residual checks should be carried out (81).

Ambulation

The traditional belief that bed rest should follow surgery was not evidence based. Bed rest promotes muscle wasting and weakness increasing the risk of pulmonary complications, and VTE (85). It follows logically that it would prolong LoS. Promoting early mobilisation counters these risks, however factors hindering patients from mobilising are numerous including; inadequate analgesia, urinary catheters, abdominal drains, and IV lines (80). Conversion to oral intake and expediting their removal facilitates easier ambulation.

Discharge pathways

Conflicting evidence is available regarding efficacy of discharge pathways in ERAS. A study in the colorectal population assessing satisfaction with ERAS discharge processes demonstrated that the majority of patients felt both (I) adequately informed regarding discharge, and (II) ready for discharge, however there were some patients who felt the post-operative information was inadequate. The authors concluded that improved education could minimise unplanned hospital reattendance in the post-operative period (86). Another study assessing patients' compliance with discharge instructions found that the critical factors were health literacy, cognition, and self-efficacy, and that protocols for identifying and managing patients at risk of poor understanding of post-operative instructions need to be implemented (87). A qualitative study assessing patients' perceptions of discharge information and the post discharge experience found that although the majority understood the content of the written discharge information, and were empowered by this, a recurring theme was that there was inadequate information on how to access healthcare providers

for advice on the acute issues that follow discharge (88). Improved post-operative education and closer follow up could reduce 49% of preventable readmissions (89).

Overall it is likely that continued refinement of discharge pathways may yield reduced readmission rates and contribute to more cost-effective care.

ERAS audit & reporting

In order to maximise benefit from the ERAS pathways, it is important to adhere to them. Without regular auditing of compliance with ERAS pathways, the degree of adherence is uncertain. A prospective study in gynaecologic oncology patients using an ERAS compliance audit tool assessed compliance with ERAS elements pre and post implementation of an ERAS protocol. This showed an increase in compliance with ERAS components from 56–77%, and a significant reduction in, complications, LoS (with no increased readmission rate) and a cost saving of $956 per patient (2).

Summary

ERAS for gynecologic oncology surgery has been shown to be safe and cost effective, with improved outcomes for patients and healthcare systems. As the evidence base evolves so will the guidelines. Emerging evidence regarding efficacy of wound catheters, fascial plane blocks, liposomal bupivacaine, and ITM may result in a reduction in epidural analgesia even for open surgery. In addition, the number of major cases that can be undertaken robotically is increasing. Further improvements in patient education and discharge protocols may reduce further readmission rates and yield further cost savings. Auditing adherence to ERAS pathways and outcomes is integral in monitoring for efficacy and safety.

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