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14. Critical care and pain management in patients who have undergone cytoreductive surgery for gynecologic malignancies

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Abstract. Surgery plays a central role in the treatment of gynaecological malignancy. It should be as complete as possible and is either performed first or after chemotherapy or neo-adjuvant radiotherapy. The role of the anaesthetist in this context is primarily to conduct a preoperative evaluation and to assess the impact of cancer on the patient. This evaluation must include the pre-operative nutritional status, occurrence of paraneoplastic syndromes, search for metastasis and obesity, which is a risk factor for most gynaecologic cancer. Chemotherapy, with deleterious side effects and drug interactions which may impact on anaesthesia, is important to evaluate before surgery. Secondary effects from these treatments most important to evaluate because of their anaesthetics' implications are haematologic, cardiologic, pulmonary and neurological toxicity. Drug interactions between cytotoxic drugs and anaesthetic agents are now well known. Nitrous oxide should be avoided as it may potentiate the effects of cytotoxic chemotherapy, halogenated agents should be used cautiously

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in case of hepatotoxicity, local anesthetics may potentiate the cardiac toxicity of anthracyclines, and cyclophosphamide has an anti-cholinesterase effect which can enhance the effect of succinylcholine. Benefits and risks of loco-regional anaesthesia should be discussed in case of chemotherapy induced neurological toxicity.

The second role of the anaesthetist is to determine the technique of anaesthesia and analgesia adapted for the proposed surgery. Either spinal or general anaesthesia may be performed for surgery in case of cancer of the cervix and endometrium. The risk / benefit balance does not appear to be in favour of epidural anaesthesia for surgery for cancer of the uterus. As the surgical treatment of ovarian cancer is very invasive and requires a laparotomy, the use of spinal anaesthesia with morphine alone or epidural anaesthesia appear to be the techniques of choice. Whereas in breast cancer, general anaesthesia is the modality of choice, the paravertebral block remains an interesting technique.

Finally, the postoperative rehabilitation must take into account the pain, which is often marked by a strong psychological component. As post operative pain is commonly intense and predictable, regular measurement of pain is fundamental, with no matter which one among several tools in a repetitive way during hospitalization. The key word of the pain management is multimodal analgesia, which might remain the gold standard. Post-hysterectomy pain is significant in the 24 to 48 hours after the procedure and necessitates aggressive analgesia which justifies opioids analgesics. Patient controlled analgesia allows the patient to treat their own pain and satisfaction is increased. The use of local anaesthetic infiltrations or bilateral ilio-inguinal block, for the management of post-operative pain is not routinely use in abdominal hysterectomy but is still useful in patients in whom morphine is contra-indicated. Spinal anaesthesia appears to be preventative of chronic pain after hysterectomy. On other hand, ovarian cancer surgery is often extensive and requires prolonged laparotomies for which regional anaesthesia is irreplaceable and should be a central element of multimodal analgesia. More over, epidural is supposed to attenuate the metabolic response to surgical stress and has a central role in the early post-operative rehabilitation, like in major visceral surgery. Continuous epidural infusion provides better analgesia than PCEA, but the use of PCEA reduces side-effects of epidural analgesia. In breast surgery, chronic pain has a high incidence of 50-60 %. The paravertebral block is an interesting alternative which can limit the side effects of nausea and vomiting associated with opioids and allows a prolonged duration of analgesia until mobilisation. Continuous infusion of local anaesthetic in the wound via a multi-perforated catheter seems an interesting alternative that is less invasive.

New literature about the influence of pain on tumour progression and the preventative effect of regional anaesthesia on tumour recurrence is now published, but had only been demonstrated on animal models. It is still interesting to keep in mind, considering post-operative analgesia.

In conclusion, anaesthetists and intensivists are frequently involved in the management of patients undergoing gynae-oncology surgery as surgery is a key part of the management. We have discussed the careful preoperative evaluation and choice of anaesthetic technique which takes into account the individual physiological reserve and also neo-adjuvant therapies. In terms of managing postoperative pain the key is in

a multimodal approach, taking into account the possibility of hyperalgesia and chronic pain and the psychological component associated with this type of pathology.

Introduction

Gynaecological cancers are frequently occurring pathologies often affecting relatively young women, whose life expectancy is improved by the evolving treatments of these cancers. The anaesthetist is increasingly faced with these patients. Expert French and American opinion [1] [2] acknowledges the central role surgery plays in the treatment of gynaecological malignancy. Surgery should be as complete as possible.

The treatment of tumours of the breast, endometrial, cervical and ovarian cancer involves invasive surgical techniques, either performed first or after chemotherapy or neo-adjuvant radiotherapy, according to the spread of disease. The role of the anaesthetist in this context is primarily to conduct a preoperative evaluation and to assess the impact of cancer on the patient who may be extremely undernourished and may have undergone intensive chemotherapy with deleterious side effects. The technique of anaesthesia and analgesia must be adapted for the proposed surgery. Finally, the postoperative rehabilitation of these immunocompromised patients must take into account their pain, which is often marked by a strong psychological component.

I. Preoperative assessment

1. Features common to gynaecological cancers

The preoperative evaluation of patients with gynaecological cancers is usually performed during the anaesthesia consultation. Ideally the consultation should be scheduled well in advance to allow for the necessary pre-operative tests to be performed and analysed, in order to assess the impact of cancer as well as pre-existing chronic disease. At the same time one must consider the semi-urgency of surgery when requesting additional investigations. In addition to the standard blood tests (full blood count, blood group determination, investigation for coagulopathy) there are some specific associated pathologies to bear in mind; gynaecological malignancies may invade the ureters and cause dilatation of the pelvi-calyceal system. Thus pre-operative investigation should include measurement of creatinine clearance and if necessary imaging of the renal tract.

Furthermore, these cancers all have a significant metastatic potential, including the lungs and spread through the lymphatics. Hence the preoperative assessment of these patients normally includes a chest x-ray to search for lung metastases and a widened mediastinum secondary to mediastinal lymphadenopathy (which can result in compression of the

tracheo-bronchial tree, vascular axis or cardiac chambers). This latter finding may justify further investigation by contrast CT and an echocardiogram. Extrinsic compression of the airway can cause tracheal or bronchial problems resulting in life threatening difficulties with intubation as well as ventilation [3] [4]. Because of the risk of liver metastasis, biochemical analysis of liver function is recommended. The preoperative evaluation of the patient must take into account the patient's nutritional status. Indeed, the pre-operative nutritional status may affect the quality of surgical scar closure, wound healing [5], resistance to infection, the occurrence of decubitus ulcers and can lead to impaired muscle function, which may impact on respiratory function post-operatively. This nutritional and metabolic status can be evaluated by weight loss (10 to 20% in 6 months being significant) or more precisely by calculating the BMI (Body Mass Index), where a value of 16 kg/m² or less indicates malnutrition. Only patients with severe malnutrition have an indication for pre-operative enteral nutrition which requires at least 7 days to be effective [6].

Pre-operative investigations include an electrocardiogram systematically performed in patients who are over 50 years. The rest of the cardio-vascular assessment should be determined individually depending on the history of cardiovascular disease and should include NYHA staging for symptoms of dyspnoea.

Paraneoplastic syndromes should be sought out: SIADH (syndrome of inappropriate secretion of anti diuretic hormone) characteristically reveals hyponatraemia, Cushing syndrome hypernatraemia, hyperparathyroidism causes hypercalcemia and Eaton-Lambert syndrome is responsible for a myasthenic picture.

At the end of the anaesthesia consultation an ASA score may be defined, the likelihood of transfusion evaluated. A frank discussion with the patient should be offered (sometimes declined) to allow the patient to discuss details of their peri-operative care (pre-medication, vascular access etc.). Specifically this should cover plans for pain relief post-operatively as well as general issues associated with anaesthesia and the possibility of transfusion [2].

2. Different types of gynaecological cancer surgery and their implications for anaesthetists

Cancer of the cervix cancer is often detected by the cervical smear and the role of papilloma virus in pathogenesis is becoming increasingly apparent. The patients are mostly young women, the peak incidence is between 48 and 55 years, and usually in good physical condition. They tend to metastasize preferentially to the liver and lungs. Epidermoid or adenocarcinomas (beyond the sub-clinical stages treated at colposcopy) are

treated according to their TNM staging [7] by vaginal hysterectomy in some cases with aortic and pelvic lymphadenectomy. The skin incision is usually of the Pfannenstiel type, but in certain cases a vaginal hysterectomy with laparoscopy may be considered.

Adenocarcinomas of the endometrium or sarcomas have a different epidemiology with over 90% of women with endometrial cancer over the age of 50 and therefore present a more fragile population. Obesity, combined with the nulliparity and diabetes, are risk factors. Anaesthetic concerns for the obese patient include vascular access, airway and ventilator management and the problem of adjusting dosages. Depending on the volume of the uterus, the invasion of myometrium, adnexae, lymph node involvement, surgery may go as far as total hysterectomy with pelvic and para-aortic lymphadenectomy. Surgery is classically performed abdominally, but the vaginal route may be reserved for frail patients. All efforts are made to prevent dissemination of tumour at operation. Adnexectomy and lymphadenectomy are performed laparoscopically.

Tumours of the ovary are mainly primitive epithelial tumours and are the fifth most common neoplasia in women (10/100 000 average incidence in industrialized countries) with a peak incidence among women 60 to 70 years. This cancer is often diagnosed late with the presence of clinical signs indicating a significant extension in the abdomino-pelvic cavity (ascites, pelvic pain, perception of a pelvic mass, occlusive syndrome). Chest radiography is used to screen for the presence of a pleural effusion that may require a diagnostic puncture. The effusion can be an inflammatory reaction to peritoneal extension of the tumour or carcinomatous pleurisy. Surgery is performed according to the consensus that the goal is complete resection of the lesions (absence of macroscopic residual) since the quantity of residual tumour correlates to survival [8]. Xyphoid-pubic midline laparotomy is the standard procedure for total abdominal hysterectomy with bilateral adnexectomy, omentectomy, appendectomy and lymph node resection infra-renally with blind peritoneal biopsies. Excision of any other resectable lesions is performed and may include segmentectomy of the bowel. Finally peritoneal lavage is performed for diagnosis and cytology of potential tumour [9]. Thus this may constitute extensive and prolonged surgery with the potential for bleeding and post-operative pain in patients who are often elderly. Chemotherapy is almost always with a platinum salt post-operatively. These patients may well undergo a 'second-look' surgery following chemotherapy, their physical status will then need to be re-evaluated.

Cancer of the vulva and vagina are more rare and tend to require more superficial (although mutilating) surgery. They will not be discussed here.

Breast cancer is the most common female cancers. It affects about one woman in eleven and is responsible for 18% of cancer deaths in women. Over 50% of cancers are observed after 65 years and nearly 10% before 35 years [10]. Obesity is associated with an increased risk of occurrence of

breast cancer. Treatment of a hypercholesterolemia should be set at least 7 days before surgery to be effective [11]. The initial surgical treatment is a lumpectomy with contemporaneous histological examination (frozen section) whose aim is to change the course of the intervention. If the nodule is a benign tumour, the intervention is stopped. If the nodule is a carcinoma, an axillary clearance is performed. A mastectomy is performed if the cancer is large or bifocal. The anaesthetic management is simple but may include a semi-sitting position for some mastectomies. This position requires that the tracheal tube is carefully secured and that attention is paid to the position and wellbeing of the arms peri-operatively.

3. Adjunctive therapies and their implications for anaesthesia

a. Dose chemotherapy deleterious side effects

Cancers of the ovary are very chemosensitive and patients often benefit from adjuvant or neo-treatments, commonly based on platinum salts. Chemotherapy also has a place in many breast cancers calls for the use of anthracyclines, taxanes, vinorelbine, platinum derivatives, fluorouracil (5FU), and cyclophosphamide. These drugs have important secondary effects as well as drug interactions which may impact on anaesthesia.

Haematologic toxicity is manifested mainly 7 to 14 days after chemotherapy. Neutropenia less than 500/mm³ should delay surgery. Thrombocytopenia less than 50 000/mm³ justifies a platelet transfusion prior to the operation. Anthracyclines [12] have a cardiac toxicity that can occur early or delayed, depending on its combination with cyclophosphamide or radiotherapy. This cardiotoxicity is increased in the presence of certain risk factors such as extremes of age, gender, combinations of cardiotoxic drugs and with pre-existing cardiovascular disease [13] [14]. The acute clinical picture varies from simple atrial extra-systoles to supraventricular and ventricular tachycardias, and to other repolarization with microvoltage disorders [15]. The most severe form is acute heart failure which appears to arise independently of the administered dose. The delayed form depends on cumulative doses (550mg/m² for doxorubicin) and consists of a dilated cardiomyopathy. The search for functional and clinical signs of heart failure should be careful in the anaesthesia consultation and deserves investigation with a 12-lead electrocardiogram, echocardiography and myocardial scintigraphy with evaluation of systolic and diastolic heart. In addition, 5FU can cause coronary spasms leading to coronary heart disease. Nevertheless, it seems that only patients with a history of congestive heart failure are likely to suffer cardiovascular complications in the peri-operative period [16].

Among the products typically used in gynaecological cancer, the taxanes have acute pulmonary toxicity that manifests in the form of interstitial pneumonitis, a bronchospasm or a pleural effusion, confirming the need for a pre-operative chest X-ray [13]. Alkylating agents and cisplatin are nephrotoxic and the most common pathology is acute tubular necrosis. Preoperative analysis of serum electrolytes and urea is performed routinely. Cyclophosphamide produces liver toxicity and investigations for cytotoxicity should be performed [17].

Signs of neurological toxicity should be documented when epidural analgesia is envisaged. This toxicity may be central (hemiplegia, cerebellar syndrome) for spindle poisons or peripheral (abolition of bone-tendon reflexes, sensitive neuropathy) for platinum, taxanes and vinca-alkaloids [13].

Digestive toxicity with nausea, vomiting and diarrhoea associated with the cytotoxic agents only exists in the hours following administration so should have no effect on airway management at the time of anaesthesia, but it is wise to look out for electrolyte disturbances.

b. Corticosteroids

Corticosteroids are often used in oncology, particularly in cases of peritoneal carcinomatosis [18]. There is a risk of acute adrenal insufficiency post-operatively requiring dose adjustment and the addition of hydrocortisone peri-operatively.

c. The chemo-hyperthermia intra-peritoneal (CHIP)

The CHIP is an intense therapy proposed in well-selected cases of localized peritoneal carcinomatosis, i.e. without evidence of visceral extension. An intraperitoneal infusion of chemotherapy combined with hyperthermia (43 ° C) follows immediately after surgical excision of the mass. This technique has severe hemodynamic consequences, and is reserved for those with no preoperative signs of cardiovascular disease.

II. Perioperative techniques and analgesia

1. Pre-emptive analgesia

Pre-emptive analgesia is a controversial subject [19]. It prevents sensitisation of both peripheral and central nervous system by the administration before surgery of NSAIDs or local anaesthetics, i.e. treating pain prior to its onset in order to decrease intensity and duration of post-operative pain. It is distinct from preventive analgesia which reduces central sensitization that arises from noxious inputs across the entire perioperative period, beyond the clinical

Table 1. Pre operative evaluation.

For all patients
<u>Interview</u> : search for signs cardiovascular dysfunction, dyspnea, palpitations, chest pain, oedema, hospitalizations for acute pulmonary oedema, cardiovascular history, impaired general condition.
<u>Clinical examination</u> : cardio-pulmonary auscultation, evaluate clinical signs of heart failure right and left, difficult intubation criteria, evaluation of venous access.
<u>Tests</u> : blood group, full blood count with platelets, coagulation profile, serum electrolytes including calcium, magnesium, phosphate, serum creatinine and blood urea, transaminases, total bilirubin free and combined, chest X-ray.
Specific investigations
<u>Neurological examination</u> : regional anaesthesia planned and history of neurotoxic chemotherapy
<u>Electrocardiogram</u> : if more than 50 years, if clinical signs of CVS disease, cardiovascular history, treatment with anthracyclines
<u>Echocardiography, myocardial scintigraphy</u> : cardiovascular history, treatment with anthracyclines, after consulting cardiologist
<u>Respiratory function tests</u> : clinical, taxanes
<u>Nutritional assessment</u> : signs of malnutrition

duration of action of the target preventive drug. One good example is ketamine, whose analgesic effect lasts very long, beyond 5 half lives. Both strategies prevent hyperalgesia. In a meta-analysis on 66 studies of general surgery, Ong *et al.* found that epidural analgesia resulted in consistent improvement on analgesic consumption, time of first rescue analgesic request, post-operative pain scores [20]. Local anaesthetic wound infiltration and NSAID administration improved analgesic consumption and time of first rescue analgesic request but not post-operative pain scores. The least proof of efficacy was found for opioids and systemic NMDA antagonist. However, ketamine, whose anti-NMDA (N-methyl-D-aspartate) receptor action is well known, appears, in a systematic review of the literature, as an effective prevention for 58% of patients in non-gynaecological surgery [21]. Regarding gynaecologic surgery, certain non-randomized studies reported 40% savings morphine post-operative [22] while another randomized study revealed no beneficial effect on the administration of ketamine before the incision of hysterectomies [23]. Another molecule, gabapentin [24], has analgesic properties in both acute and chronic pain. Oral premedication with gabapentin reduces morphine consumption post-operatively through a central mechanism of action by activation of spinal descending noradrenergic tracts [25]. Gabapentin also decreases hyperalgesia and the risk of subsequent chronic pain through its calcium channel antagonist effect.

2. Drug interactions between cytotoxic drugs and anaesthetic agents

Anaesthesia of such patients may be complicated by the underlying patient state and their chemotherapy. Firstly, peri-operative monitoring will be adapted according to any cardiovascular history of the patient. No particular anaesthetic technique has demonstrated its superiority in terms of reducing occurrence of cardiovascular events per-operatively [16]. However there are some precautions with the use of anesthetic drugs. Nitrous oxide should be avoided as it may potentiate the effects of cytotoxic chemotherapy on bone marrow aplasia. Halogenated agents should be used cautiously in case of hepatotoxicity secondary to chemotherapy, and isoflurane may possibly lengthen QT segment of patients on anthracyclines. Local anesthetics also potentiate the cardiac toxicity of anthracyclines, and less toxic amides should be preferred. Cyclophosphamide has an anti-cholinesterase effect for up to one month after treatment, which can enhance the effect of succinylcholine [26]. Altogether it is preferable to employ curares metabolized through Hoffmann degradation (as atracurium and cis-atracurium) and monitor their effects. In case of kidney failure or nephrotoxic chemotherapy, it is desirable to ensure proper hydration, avoid use of nephrotoxic drugs, and to adjust the doses of drugs according to renal function including antibiotics. Finally, the benefits and risks of regional anaesthesia should be discussed in case of chemotherapy induced neurological toxicity.

3. Anaesthesia and analgesia techniques according to type of surgery

The treatment of cancer of the cervix and endometrium is total hysterectomy which can be performed as an open procedure or vaginally. Several studies show a high level of postoperative pain following hysterectomy, especially by laparotomy [27] [28] [29]. Pain is at its most intense in the first 48 hours after the operation. Many articles seek to highlight the influence of anaesthesia technique on post-operative pain. In a randomized study on patients undergoing abdominal hysterectomy, the use of a spinal with bupivacaine alone before inducing general anaesthesia, can reduce the consumption of morphine PCA in patients without reducing its sides effects [30]. In the same way, spinal anaesthesia can reduce the consumption of morphine following vaginal hysterectomy but the difference is only significant for the first 12 hours in a Canadian study [31]. Intrathecal morphine requires careful monitoring to detect the occurrence of respiratory

depression, but an intrathecal dose of less than 200 micrograms does not change the respiratory risk compared with other traditional routes of morphine administration. In conclusion, spinal or general anaesthesia may be performed for hysterectomy to resect neoplasia. Combined spinal-epidural anaesthesia with post-operative use of the epidural catheter seems excessive given the intensity of post-operative pain but can be used. Studies on the early rehabilitation after colonic surgery show benefit of the use of epidural versus general anaesthesia on post-operative recovery. However, the beneficial role that epidural analgesia provides is widely reduced when part of a broader early rehabilitation program (fast track surgery) [32]. Thus the risk / benefit balance does not appear to be in favor of epidural anesthesia for surgery for cancer of the uterus.

Surgical treatment of ovarian cancer is very invasive and it requires a laparotomy often with midline incision extending above the umbilicus. This results in painful post-operative rehabilitation similar to upper GI surgery. This explains why perioperative management of ovarian cancers is based on protocols for post-operative rehabilitation of colon cancer surgery [33]. Intrathecal morphine is sometimes used and produces analgesia of good quality but of too short duration (24 hours). The recommended dose of morphine is about 0.1 to 0.3 mg. By epidural or intrathecal route, morphine does not cause sympathetic or motor block. With the highly lipid-soluble sufentanil or fentanyl, onset and duration of action is much shorter than for morphine (from 3-6hrs compared to 12-24h). The duration of intrathecal analgesia is limited to the duration of the product used. The addition of adrenaline can be used to increase duration of analgesia without significantly increasing side effects [34]. Clonidine has similar properties but increases the risk of sedation and hypotension [35]. Side effects such as respiratory depression, nausea and urinary retention, are dose-dependent which also justifies the use of the lowest effective dose possible. The same effects are found for the use of opiates by epidural route but with a lower frequency [36]. Thus the use of epidural anaesthesia started perioperatively appears to be the technique of choice. Epidural analgesia should combine an opioid and a local anaesthetic. The site of puncture should be low thoracic with high concentration of local anaesthetic to reduce motor block and hypotension, compare to lumbar epidural which will need bigger volume for the same level of anaesthesia. It must often be accompanied by general anaesthesia because the first step of the procedure often involves laparoscopy, and general anaesthesia is indicated for patient comfort for cases where surgery may be prolonged.

Optimal treatment for ovarian cancer peritoneal deposits is not well established with weak responses to second line chemotherapy or beyond.

In this context cytoreductive surgery associated with peritoneal chemotherapy has been proposed [37]. These operations are long (8 hours on average), invasive (xyphoid-pubic incision) and extremely painful post-operatively. These patients benefit from epidural during the perioperative period. Perioperative management is fairly standard [38], and includes large bore venous access, invasive arterial monitoring, central venous pressure trace and cardiac output (usually by oesophageal Doppler or transoesophageal echocardiography). Such invasive monitoring is warranted because of the haemodynamic variations created by a large third space fluid compartment and large insensible losses secondary to intestinal resection. Hypotensive episodes limit the perioperative use of the epidural. Hyperthermia itself is responsible for an increase in insensible losses, an augmentation of microvascular permeability and hypoalbuminaemia, and a reduction in systemic vascular resistance, all of which increase perioperative hypotension. These effects can be offset by carefully guided filling. Both bladder and oesophageal temperatures should be monitored. The liver is also sensitive to hyperthermia which may result in altered pharmacokinetics of anaesthetic agents, notably shortening duration of neuromuscular blockade with vecuronium. A transitory increase in creatinine is expected and may also be offset by maintenance of renal perfusion intraoperatively as well as encouraging diuresis. In addition the detrimental effects of the chemotherapy on diaphragmatic excursion can be countered by using ventilation with PEEP. Finally, it is important to watch out for a coagulopathy secondary to the thermal insults especially at the end of the procedure.

With breast cancer, general anaesthesia is the modality of choice. This is due to the location of the surgery which would require a thoracic epidural if an awake technique were considered, which is thought to be too invasive and uncomfortable for the patient to justify its routine use. Analgesia is usually provided by a multimodal combination of non opioids and morphine. Paravertebral block may provide very potent anaesthesia [39] but is an invasive technique with risk of pneumothorax (1% in the literature) and with a high failure rate in adults (10.7%) [40] and thus is usually used when morphine is contraindicated. Local anaesthetic creams may also be of use when applied before surgery (See below).

4. Perioperative fluid therapy

Patients are required to be fasted for 6 hours for solids prior to elective surgery to ensure an empty stomach. Many studies have shown a benefit from allowing clear liquids to be drunk up until two hours before surgery in terms of reducing postoperative complications [41] [42]. It is imperative to find a

balance between a restrictive fluid therapy which reduces cardiopulmonary complications which may result in hypovolaemia and a liberal fluid strategy which reduces nausea and vomiting [43] but at the same time may increase hyperchloraemic acidosis [44] [45] and post-operative morbidity and hospital stay in major abdominal surgery [46]. The optimal strategy is “goal directed fluid administration” whereby cardiac index and oxygen delivery are targeted using colloids to decrease the amount of fluids infused [47].

5. Prophylactic antibiotics

Antibiotic therapy should be adjusted to local microbiological cover as well as to suit the type of surgery. The principal agents are penicillins and usually amoxicillin in combination with clavulanic acid. Patients that have a history of recent admissions to hospital may have nosocomial pathogens and adjusting antibiotics accordingly may be required.

6. Cell salvage

Autotransfusion of patients' own blood retrieved from the perioperative fields is a controversial issue in cancer surgery as it theoretically exposes the patient to the risk of reinjecting tumour cells into the circulation. There is no rigorous randomised controlled trial in the literature but a review [48] demonstrated that in all of the studies (theoretical and clinical) tumour cells are found in the salvaged blood and in the reinjectate. However, the use of the Cell Saver in six clinical studies with 20 to 55 patients each has not led to dissemination after a 12-60 months follow up [48]. The use of a leucocyte filter significantly reduces the quantity of tumour cells in the salvaged blood whilst irradiation of the blood with 50 Gy prevents further cellular division. At present routine use of the cell saver is not advised with the exception of unexpected haemorrhagic cancer surgery, and then with the use of a leucocyte filter.

III. Postoperative management

1. Pain

As post operative pain is commonly intense and predictable [49], post operative care must at first take care of pain relief. A fast recovery is essential to reduce complications related to surgery and prolonged bed-rest and to reduce postoperative morbidity [50]. Gynaecological cancer surgery results in pain with a psychological component [51]. Regular autoevaluation of pain is fundamental to understanding and managing postoperative pain. Pain can be measured using scales which can be verbally reported or expressed by a mark on a line 100mm long (visual analogue scale, VAS). Pain intensity can

be recorded by best-fit description (no pain, moderate, strong, severe, excruciating) or more precisely using a verbally reported score of 0 to 10 (numeric reporting scale NRS, verbal reporting scale VRS) where 10 is defined as the worst ever experienced pain and 0 as no pain. The advantage of using continuous scales is that it is more precise in registering pain responses to therapy (for example addition of a non-steroidal anti-inflammatory alone is unlikely to change a descriptive pain from one category to the next, but may commonly result in a demonstrable change in numeric reporting scale or VAS) [52]. The most important thing is to use these tools systematically and in a repetitive way during hospitalization. It should be noticed that there is a large inter-individual variability in pain which also follows a diurnal course (maximal in the morning and evening) [53]. This should be taken into account when managing pain.

Gabapentin is used more and more as part of a pre-medication, and has been used for control of pain after hysterectomy [54] where it has an opioid reducing action but at the price of increasing sedation. Multimodal analgesia with two or three different non-opioid analgesics will limit the side effects of each product (for example anti-inflammatory and paracetamol). Non-steroidal anti-inflammatories should be given provided there are no concerns about renal function or coagulation. The pharmacokinetics of these agents mean that they are given orally pre-operatively and as soon as the oral route becomes possible post-operatively [55]. Treatment of post-operative pain continues in the anaesthetic recovery room and is usually based on morphine titration according to local protocol [56] which leads to rapid establishment of analgesia. The posology of morphine must be adapted according to the patient's renal function especially considering that some will require prolonged opioid therapy.

A novel concept is emerging in the literature of the influence of pain on tumour progression and of the preventative effect of regional anaesthesia on tumour recurrence [57] [58] [59] [60]. These effects have been well demonstrated on animal models while human studies, although encouraging, have still many limitations to conclusively prove a benefit [61].

a. Specific to hysterectomy

Post-hysterectomy pain is significant in the 24 to 48 hours after the procedure and necessitates aggressive multimodal analgesia [29] including opioid analgesics. As before, morphine can be given by the intrathecal route, orally or parenterally (sub-cutaneous, intra-muscular) or intravenously using a controlled administration system (patient-controlled analgesia, PCA). The speed of action and its bioavailability depend on route of administration. By using intravenous titration, one can rapidly establish analgesia on an individual basis [56] after which therapy can be continued by PCA or via

intermittent injection. The latter is probably the most simple way to provide analgesia as long as the injections are performed regularly [62]. However this technique may be limited by pain between injections, a delay in action and a variable absorption in the post-operative period. The reduced satisfaction experienced with this technique is probably due to a mis-evaluation of the pain intensity of the patient by the nursing staff [63]. Patient controlled analgesia allows the patient to treat their own pain according to parameters set by the doctor. This method allows instant analgesia and relies far less on the immediate presence of nursing staff. With this technique the patient will tolerate higher pain scores as she is in control of her own analgesia [64] and satisfaction is increased [65]. It has been shown that PCA increases the frequency of urinary retention in the first 24-hours after pelvic surgery [66]. Therefore a urinary catheter is usually required for the first 24-72 hours after hysterectomy.

If epidural or combined spinal-epidural anaesthesia during surgery is used, then the epidural is used post-operatively for analgesia, which is extremely efficient for controlling pain on rest and on movement. The use of a patient-controlled epidural analgesia program has been shown to reduce secondary effects such as motor block and nausea and vomiting compared with a continuous infusion [67]. There probably also exists a role for pre-emptive epidural analgesia followed by general anaesthesia for the control of immune response in the post-operative period [58].

For several years there has been increasing interest in the use of local anaesthetic infiltrations for the management of post-operative pain [68]. There are numerous studies looking at the beneficial effects of local anaesthetic infiltration. The large diversity of routes of administration (wall blocks, sub-cutaneous infiltration by catheter, sub-peritoneal route, continuous infusion and boluses) and the various products used make the interpretation of these results difficult. Specifically for abdominal hysterectomies it seems that the beneficial effect on the VAS is not large enough to justify routine use of infiltration catheters [69] [70] [71] [72]. In a double-blind study of patients undergoing abdominal hysterectomy the morphine sparing effect of parietally infiltrated bupivacaine is only significant in the first 4 hours after surgery compared with a placebo control [73]. Numerous placebo-controlled studies have demonstrated that parietal infiltration alone of local anaesthetic after hysterectomy has no analgesic role [72] [74] [75] [76]. However, if this infiltration is performed preemptively then 8 hours morphine sparing effect is noted compared with placebo [77]. On the other hand, some techniques employing local anaesthetics have proven their advantages. Bilateral ilio-inguinal block has been shown to lead to reduced morphine consumption for 2 days following surgery but disappointingly

this is not associated with any reduction in morphine related side effects [78]. In laparoscopic cases, instillation of local anaesthetic directly on the sub-diaphragmatic and operative sites by the surgeon is a simple technique. The morphine reducing effect is significant in the first 24 hours [79]. To conclude, it seems still useful to remain aware of these developing techniques and they certainly have a role in combination with non opioids drugs.

Chronic pain affects 5-32% of women undergoing hysterectomy for non-neoplasia pathology [80]. The mechanisms underlying this type of pain are not entirely elucidated but include factors triggering central nervous system sensitization and hyperalgesia. It is associated with intra-operative nerve lesions and an inflammatory response. Risk factors include the intensity of pain pre and post-operatively, as well as the genetic and psychosocial profile. It is apparent that the psycho-affective dimension of cancer surgery places the patients at high risk of developing chronic pain. Spinal anaesthesia appears to be preventative of chronic pain using multivariate analysis in one non-randomised study [81]. In the only available randomised trial [Sprung, 2006 #48], it seems that the use of intrathecal morphine decreases pain two weeks after vaginal hysterectomy, however, without effect on either length of hospitalization or patients' postoperative functional status. It has also been shown that epidural anaesthesia reduces chronic pain in major surgery in a non-randomised trial [82].

b. Specific to ovarian cancer

Ovarian cancer surgery is often extensive and requires prolonged laparotomies for which regional anaesthesia is irreplaceable. In a meta-analysis of all the randomised studies comparing the efficacy of epidurals and PCA morphine on postoperative analgesia, epidurals are demonstrably superior at all stages [67]. It is important to realise that continuous epidural infusion provides better analgesia than PCEA, and that the use of PCEA reduces drug consumption and side-effects of epidural analgesia. Sole agent use of local anaesthetics in the epidural infusate has been shown to be superior to opioids alone via the same route [67]. However, the combination of an opioid with a local anaesthetic agent (bupivacaine or ropivacaine) is the best means of increasing analgesia and of reducing tachyphylaxis which inevitably arrives with local anaesthetics as sole agents after 12-36 hours of administration. It would appear that there is a real benefit in establishing epidural analgesia pre-emptively before incision [83], by associating local anaesthetic agent and opioid, which will decrease post operative pain scores and systemic morphine consumption. Combinations of local anaesthetic and opioid demonstrate a synergistic effect [84], allowing for a reduction in dose

of both products. Such an epidural mixture allows excellent analgesia to run for several days in the post-operative period. In abdominal surgery numerous studies have demonstrated the superiority of the epidural route for analgesia [85] and for attenuating the metabolic response to surgical stress [86] which translates into a significantly reduced operative risk [87]. It also allows a faster recovery and better comfort for the patients [88]. The use of epidural opioids excludes opioids being administered by any other route according to the duration of action epidurally. However, duration of action may be short and patients may start to suffer well before reaching the mean duration time of the product. It is therefore essential to anticipate with an emergency prescription of analgesic which may include morphine injection. This is also best avoided by regular systemic administration of non opioids added to the epidural regimen. This is the method of analgesia described in the largest series of early post-operative rehabilitation for major visceral surgery [89]. This multimodal approach influences recovery and morbidity for patients in conjunction with simple measures which do not have any impact individually [32]. Numerous post-operative techniques are perpetuated by habit and go against current evidence such as the continued use of gastric tubes, abdominal drains, urinary catheters, dietary restriction and bedrest. Gastric tubes can increase chest infection rates and should not be maintained in place after gastrointestinal resection. It is now universally agreed that the resumption of oral feeding should be achieved as soon as possible [90], above all in the context of neoplasia and malnutrition. Epidural analgesia allows for early mobilisation in giving high quality analgesia on movement as well as at rest. The urinary catheter should not be a barrier to early mobilisation with epidural analgesia and can be removed expectantly at 24 hours. Early mobilisation counters the negative effect of bedrest which increase loss of muscle mass, affects respiratory function and predisposes to thromboembolism. Mobilisation will be facilitated by using low concentrations or low volumes in epidural, which limit motor block.

Finally, the use of regional analgesia does not necessitate abandoning other analgesics but on the contrary, regional anaesthesia should be the central element of a multimodal analgesia [91]. This multimodal analgesia can employ numerous molecules having additive or synergistic actions thus reducing opioid consumption and opioid side effects. Various adjuvants can be used separately or combined, and should be started from the beginning of the procedure: paracetamol, nefopam, NSAIDS, ketamine, clonidine, gabapentin, magnesium, intravenous lidocaine [92] [32] [93]. Where epidural analgesia is not used, a multi-holed catheter inserted by the surgeon just after peritoneal closure may lead to satisfactory analgesia, as apparent in studies of visceral surgery [94]. This differs from hysterectomy because the wound is

larger than the pfannenstiell incision and vertical which is supposed to be painful especially during mobilisations.

c. Breast surgery

A wide range of surgical procedures may be encountered. For simple, minor procedures, analgesia is managed by oral non-opioid combinations. For simple mastectomy without lymph node removal, Fassoulaki et al [95] have shown the analgesic efficiency of local anaesthetic cream (EMLA) applied to the surgical site before surgery. The cream is applied all around the surgical zone pre-operatively by the nurse preparing the patient and is continued for 4 days post-operatively. Above all this study showed that this technique can significantly reduce chronic pain. Chronic pain has a high incidence of 50-60 % following the usual management of these cases, but was reduced to 22% in this study. These results need to be confirmed but are very promising at this stage. In extensive breast surgery (radical mastectomy), regional anaesthetic techniques are useful and are associated with better analgesia than PCA [96]. Perioperative use of an epidural infusion also results in less blood loss which adds another advantage to these techniques. Placement of a paravertebral catheter is an interesting alternative which can limit the side effects of nausea and vomiting associated with opioids and allows a prolonged duration of analgesia until mobilisation [40] [97]. These analgesic techniques are very effective but their use is still limited in breast surgery. Indeed paravertebral blocks are an expert technique and as breast surgery has become less invasive in the last few years, the perceived benefit of performing these complex and invasive procedures is lesser. The continuous infusion of local anaesthetic via a multi-perforated catheter in the wound seems an interesting alternative that is less invasive and equally effective compared to a 'single-shot' paravertebral technique [98].

2. Deep vein thrombosis (DVT) and pulmonary embolism (PE)

The association between cancer and hypercoagulability is well known, due to certain factor growth (V, VIII, IX, XI), disseminated intravascular coagulation (DIC) and a reduction in antithrombotic factors (protein C, protein S, and antithrombin). Thromboembolic risk may also be raised by the simultaneous administration of chemotherapy and hormone therapy. Moreover, cancer surgeries may be prolonged and intraperitoneal, both factors which increase thrombosis. The incidence of postoperative DVT, clinically diagnosed, is 15-28% according to studies. Prevention of postoperative DVT includes graduated compression stockings (established

pre-operatively) as well as low molecular weight thromboprophylaxis for four weeks, eg. 40mg enoxaprine sub-cutaneously [99] started 6 to 8 hours after surgery.

3. Antibiotics

Patients who have had chemotherapy pre-operatively should be considered as immunocompromised and may receive 48 hours of prolonged antibioprohylaxis.

4. Prevention of postoperative nausea and vomiting (PONV)

There is no evidence of an increased incidence of nausea and vomiting in patients on chemotherapy [100]. Thus there are no particular preventative measures to be taken in the context of prevention of nausea and vomiting in this group. Factors that pre-dispose to PONV are well-known and are included in the Apfel score; female sex, non smoker, history of travel sickness and requiring morphine postoperatively. It is notable that most patients undergoing gynaecology surgery will have a score of at least 2, i.e. a 40% risk of nausea-vomiting, which justifies the use of a preventative therapy, including at least antiemetic drug. This regimen should be based on a multimodal approach if risks factors are found.

5. Severe malnutrition

Artificial nutrition in the postoperative period is indicated for the malnourished, if it is unlikely that they will be able to recover a diet that covers at least 60% of their nutritional requirements within a week of their operation, or in the case of a complication that results in a prolonged period of starvation or in the event of hypermetabolism [101]. The route should be enteral whenever possible. Traditionally, post-operative oral intake is withheld until the return of bowel function in a way to avoid vomiting, pneumonia, wound dehiscence and anastomotic leakage. In gastrointestinal surgery there is a trend for commencing to feed from the first post-operative day before the return of bowel function. It seems logical to do the same for gynaecological surgery all the more so if there has been non surgical disruption of the digestive tract. The idea is to reduce length of stay and post-operative complications associated with extensive surgery [102] [103] [104]. This notion is confirmed in a review of the literature published in 2007 [105], on randomised controlled trials that compared the effect of early versus delayed initiation of oral intake of food and fluids after major abdominal

gynaecologic surgery. Early feeding was defined as having oral intake within the first 24 hours after surgery. It seems that early feeding is safe, however associated with the increased risk of nausea, and a trend to reduce length of hospital stay in four studies. Empirically, patient's satisfaction should be increased, as long as this approach is individualised, but this hasn't been studied so far.

6. Effect on quality of life of multiple excisions

The management of patients undergoing gynae-oncology surgery includes evaluation of the quality of life after surgery, and measures the change in quality of life that are procedure specific eg. splenectomy, multiple gastrointestinal resections and short-bowel syndrome.

7. Specific to intraperitoneal chemotherapy

The post operative period is often marked by the occurrence of respiratory complications of variable degree [37] [38] necessitating obligatory monitoring in an intensive care unit. Ileus is common and of variable duration, early feeding being assured by jejunostomy. Finally, the surveillance for thrombocytopenia must not be forgotten. Often platelet count reaches its nadir at 5 days, which may affect the timing of withdrawal of the epidural catheter.

Conclusion

Anaesthetists and intensivists are frequently involved in the management of patients undergoing gynae-oncology surgery as surgery is a key part of the management. This surgery is sometimes performed during a window of a course of chemotherapy or radiotherapy. We have discussed the careful preoperative evaluation and choice of anaesthetic technique which takes into account the individual physiological reserve and also neo-adjuvant therapies. In terms of managing postoperative pain the key is in a multimodal approach. In fact all the analgesic techniques, infiltration, regional, systemic, pre emptive or preventive have specific advantages and disadvantages. These must be balanced against the intensity of postoperative pain and the possibility of hyperalgesia and chronic pain. As a result it is the combination of techniques and analgesics, with respect to their contra-indications, which provides the key for the optimal management of pain in these patients, without forgetting the psychological component associated with this type of pathology.

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