Royal College of Obstetricians & Gynaecologists

Management of Ascites in Ovarian Cancer Patients

Scientific Impact Paper No. 45
November 2014

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1. Introduction

Malignant ascites is the build-up of large volumes of fluid in the peritoneal cavity secondary to cancer. In the absence of malignancy, liver disease is responsible for over 80% of cases of ascites. Patients with ascites present with distended abdomen, difficulty mobilising, shortness of breath, fatigue and altered bowel habit. For ovarian cancer patients, the onset of ascites makes them feel unwell and they often describe ascites as the worst experience of their cancer journey.[1] Ovarian cancer has been described as the 'silent killer'[2] due to the minimal number of symptoms associated with it at diagnosis. However, for patients who do not present with ascites initially but develop ascites at disease relapse, it can be the first visible manifestation of their disease. This Scientific Impact Paper sets out to describe the aetiology, therapeutic options and research needs for the management of malignant ascites secondary to ovarian cancer.

2. Aetiology

Ascites is a central oedema where fluid accumulates in the peritoneal cavity.[3] In the absence of disease, around 50–100 ml of fluid every hour passes from the peritoneal cavity into the lymphatic vessels and through the lymphatic vessels in the diaphragm due to changes in pressure as a result of breathing.[4] The underlying physiological process causing malignant ascites is often multifactorial and may be due to obstruction of lymphatic drainage preventing absorption of intra-abdominal fluid and protein, disease producing a high volume of fluid with a high protein content, hypoproteinaemia and occasionally portal hypertension secondary to hepatic cancer.

Ascites can be split into two main groups: exudates which are high in protein, and transudates which are low in protein.[3,5] Exudates are more common and derive from a combination of increased permeability of capillaries and lymphatic obstruction, whereas transudates are likely to arise where liver metastases cause portal hypertension. Nonmalignant ascites is more likely to produce a transudative ascites where there is a marked increase in production of fluid and the lymphatic system reaches capacity with flow rates of 200 ml of ascites per hour.[4] Ascites resulting from compression of the hepatic vein causing portal hypertension will also produce a transudative ascites. In malignancy that has spread to the peritoneal cavity, an exudative ascites is produced and lymphatic flow markedly decreases to levels as low as 15 ml per hour as the lymphatic vessels have become obstructed by tumour[4] and cannot cope with the increased permeability of blood vessels, hence fluid accumulates. In patients with ovarian cancer, liver metastases are less common; thus an exudative ascites is expected.

3. Evidence

There is a paucity of reliable evidence regarding the optimum method of managing malignant ascites either at initial presentation, during treatment or palliation. Extensive electronic literature searches indicate that there are no randomised controlled trials, a very small number of uncontrolled prospective studies and less than 30 retrospective case series examining different management strategies for malignant ascites. The vast majority of studies have evaluated the outcomes of peritoneovenous shunts.

Management of malignant ascites is by drainage, rarely by diuretic therapy and, if recurrent, occasionally by permanent indwelling catheters or peritoneovenous shunts. There is little evidence around the use of drainage catheters to achieve optimum drainage with most research addressing the use of peritoneovenous shunts. Furthermore, there is very limited evidence on the impact of ascites on patient wellbeing or patient understanding of the aetiology of ascites.

3.1 Symptomatic drainage of ascites

Clearly, patients who have significant ascites derive symptomatic relief from percutaneous drainage. Five observational case series were identified and the number of patients included varied from 15 to 300.[6–10] Management varied, with some case series including patients receiving intravenous fluid replacement during drainage while others received no fluid supplementation. The speed of drainage varied from 15 minutes to over 24 hours. Outcome measures differed, with some reporting hypotension rates and others significant morbidities associated with the procedure. Only one study, by Gotlieb in 1998,[9] assessed the physiological response and found that a median of 4.5 litres of fluid could be drained over 30–90 minutes without changes to electrolytes, cardiovascular effects or the need for intravenous therapy. However, this was a small study with only 35 paracenteses in 15 patients.

It is common practice to perform paracentesis under ultrasound control to identify the deepest pool of fluid and to ensure that there are no vital organs beneath the drainage site. Drainage catheters are usually placed following an ultrasound to mark an appropriate area into which the drainage catheter can be introduced. The catheter can be inserted at the same time as the scan or, more commonly, afterwards on the ward.[11] The period between drainage and ultrasound can be a number of hours, in which case the bowel may have moved, making bowel perforation an increased risk. Furthermore, catheter insertion on the ward is often performed by junior doctors and the fluid is drained over a 24-hour period, requiring a median length of 3 days of hospital stay (range 1–13 days).[12,13] Some audits have recommended placement of the catheter at the time of imaging to reduce the delays in drainage and increase the speed of drainage.[12] However, there are no controlled trials in symptomatic patients demonstrating that blind drainage of ascites has a worse outcome than radiologically guided drainage.

In a survey of the management of malignant ascites in the UK involving 492 physicians and nurses, inpatient treatment was common, with only 12.8% of patients staying less than 12 hours.[11] The cost for a 3-day admission has been estimated at £1473–3146, compared with £954–1457 for outpatient treatment.[12,13] Macdonald[11] found little consensus in a survey on the type of drain, rate of drainage and use of ultrasound. This lack of evidence for optimal management was similar to that reported in earlier surveys of practice in the UK[14] and Canada.[15] More research is needed with a larger group of patients before outpatient drainage can be recommended.

There is professional consensus that prompt treatment after initial presentation either by primary cytoreductive surgery or neoadjuvant chemotherapy will minimise the development of irreversible fluid/electrolyte imbalances that might jeopardise the patient's ability to tolerate primary treatment. Patients who are systemically unwell due to hypoalbuminaemia secondary to ascites require experienced medical/nursing support to optimise their condition.

3.2 Indwelling catheters

In cases of recurrent or refractory ovarian cancer, indwelling catheters are used for patients whose ascites builds up rapidly and where it is hard to remove the drainage catheter due to excessive fluid production. In these cases there may be a need to leave a drainage catheter in situ, which the patient can be discharged with. While studies have demonstrated that indwelling catheters prevent admissions/hospital visits for further drainage, they have problems with increased infection risks and blockage.[16] The majority of case series are small observational studies. There is clearly no evidence that indwelling drains have an impact on survival. The National Institute for Health and Care Excellence published guidance promoting their use in recurrent ascites, although according to their calculations they cost more than outpatient drainage.[13] However, the true costs of ascitic drainage care in the primary care setting need to be reassessed as most patients will have existing community palliative care nursing. There is limited evidence on the acceptability of these drains for patients. In a study by O'Neill et al., 16 out of 40 patients approached to join a study of indwelling catheters

refused to enter the study, preferring intermittent drainage.[16] A small qualitative study of five patients with indwelling catheters showed that, overall, the experience was positive for those patients who had agreed to have an indwelling catheter.[17]

3.3 Diuretic therapy

There is limited evidence supporting a role for diuretics such as spironolactone in malignant ascites, with only a handful of small case series reporting the outcomes after oral or intravenous therapy. However, surveys of clinical practice suggest that diuretics are commonly used. Success has been demonstrated by daily weight loss;[18] however, Pockros et al.[19] suggested that the outcome of therapy depended on whether there was a significant gradient between ascitic and plasma albumin concentrations. Again, Pockros et al.[19] suggested that diuretic therapy was unlikely to mobilise ascitic fluid and any weight loss was from loss of fluid outside of the peritoneal cavity and could lead to patients becoming dehydrated if not carefully supervised. Palliative care physicians are more likely to use diuretic therapy initially,[11,14] assuming it is less invasive, yet patients find drainage very acceptable due to the relief it brings for a temporary inconvenience.[1] A prudent approach may be to perform serum albumin ascitic gradient (SAAG) at the first episode of symptomatic ascites requiring drainage if there is any doubt that the origin is not malignant. If the SAAG supports a transudative mechanism, then a trial of diuretics may be considered, under close observation. Further research is required to assess the effectiveness of diuretic therapy.

3.4 Peritoneovenous shunts

Peritoneovenous shunts were initially designed for use in recurrent ascites secondary to liver cirrhosis. They drain fluid into the vena cava and have a one-way valve that prevents reflux of blood. There are two shunts commonly used: the Denver and LeVeen, which require different pressures to open the one-way valves. These devices obviously spare women with recurrent ascites repeated drainage and the resultant loss of fluid and protein. They should only be considered when conservative management is unlikely to be effective and the patient's life expectancy is considered to be long enough to justify the potential morbidity of insertion.[20]

A novel battery-operated system, automated low-flow ascites pump (ALFApump®, Sequana Medical AG, Zurich, Switzerland), placed subcutaneously, moves ascites from the peritoneal cavity to the bladder via a drain. Initial study in patients with liver disease has shown the pump to be efficacious, but the safety is still moderate with high complication rates associated with insertion, catheter dislodgement and infection. Its insertion requires surgical intervention under general anaesthesia.[21]

3.5 Anti-neoplastic therapy

Tumours which are still responsive to anti-neoplastic therapy are likely to result in the prevention of further ascites build-up. While a number of drugs have been developed to target ascites, most have failed to be endorsed through randomised controlled trials. In the 1990s, tumour necrosis factor (TNF) gave promising results in early case series[22] but a randomised controlled trial showed no effect on the build-up of ascites.[23] Anti-angiogenesis drugs, such as batimastat,[20] have been trialled in early phase studies and again looked promising but trials were stopped early due to bowel obstruction. Catumaxomab (Removab®, Neovii Biotech GmbH, Graefelfing, Germany) is a monoclonal bispecific antibody approved in 2009 in the European Union for the intraperitoneal treatment of patients with malignant ascites.[24] A phase II/III clinical trial[25] compared the efficacy of catumaxomab plus paracentesis (C + P) to paracentesis alone (P) in 258 patients with recurrent chemoresistant adenocarcinoma (ovarian, gastric, breast, pancreas, colon, and endometrial) presenting with ascites. In the ovarian cancer arm, the median puncture-free survival, defined as the time after treatment (day 0) to the first need for further drainage, or death, whichever occurred sooner, was 52 days for C + P versus 11 days for P alone ($P < 0.0001$). This suggests that catumaxomab functions relatively rapidly to

alleviate ascites accumulation. Similarly, the median time to next paracentesis was significantly longer in the C + P group (71 versus 11 days; $P < 0.0001$). This represented a six- to seven-fold prolongation and would be highly beneficial to patients since ascites has a high morbidity and repeated paracentesis increases the risk of infection, bowel perforation and adhesions. Further randomised controlled trials are needed to explore the role of such agents in clinical practice.

4. Opinion

Ideally, experts in gynaecological surgical and medical oncology should initiate clinical trials to establish best practice in ascites management. In the meantime, consensus guidelines should be developed to standardise and assure the quality of practice. National guidance would facilitate training for both doctors and specialist nurses. Two key areas which need further evaluation are outpatient drainage and indwelling catheters. Until then, we would suggest drainage following insertion of the drain under ultrasound guidance (rather than afterwards). Diuretic therapy should only be considered in transudative ascites.

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Conflicts of interest: None declared.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2017, unless otherwise indicated.

