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Eleje GU, Eke AC, Igberase GO, Igwegbe AO, Eleje LI

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[Intervention Review]

Palliative interventions for controlling vaginal bleeding in advanced cervical cancer

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 5, 2015.

Cervical cancer is the fourth most common cancer among women worldwide, with estimated 569,847 new diagnoses and 311,365 deaths per year. However, incidence and stage at diagnosis vary greatly between geographic areas and are largely dependent on the availability of a robust population screening programme. For example, in Nigeria, advanced-stage disease at presentation is common (86% to 89.3% of new cases), whereas in the UK, only 21.9% of women present with International Federation of Gynaecology and Obstetrics (FIGO) stage II+ disease. Women with advanced cancer of the cervix often need palliation for distressing symptoms, such as vaginal bleeding. Vaginal bleeding can be life threatening in advanced disease, with an incidence ranging from 0.7% to 100%. Bleeding is the immediate cause of death in 6% of women with cervical cancer and its management often poses a challenge.

Thus, vaginal bleeding remains a common consequence of advanced cervical cancer. Currently, there is no systematic review that addresses palliative interventions for controlling vaginal bleeding caused by advanced cervical cancer. A systematic evaluation of the available palliative interventions is needed to inform decision-making.

Objectives

To evaluate the efficacy and safety of tranexamic acid, vaginal packing (with or without formalin-soaked packs), interventional radiology or other interventions compared with radiotherapy for palliative treatment of vaginal bleeding in women with advanced cervical cancer.

Search methods

The search for the original review was run in 23 March 2015, and subsequent searches for this update were run 21 March 2018. We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 3) in the Cochrane Library; MEDLINE via Ovid to March week 2, 2018; and Embase via Ovid to March week 12, 2018. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of review articles, and contacted experts in the field. We handsearched citation lists of relevant studies.

Selection criteria

We searched for randomised and non-randomised comparative studies that evaluated the efficacy and safety of tranexamic acid, vaginal packing (with or without formalin-soaked packs), interventional radiology or other interventions compared with radiotherapy techniques for palliative treatment of vaginal bleeding in women with advanced cervical cancer (with or without metastasis), irrespective of publication status, year of publication or language in the review.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. We found no studies for inclusion and, therefore, we analysed no data.

Main results

The search strategy identified 1522 unique references of which we excluded 1330 on the basis of title and abstract. We retrieved the remaining 22 articles in full, but none satisfied the inclusion criteria. We identified only observational data from single-arm studies of women treated with formalin-soaked packs, interventional radiology or radiotherapy techniques for palliative control of vaginal bleeding in women with cervical cancer.

Authors' conclusions

Since the last version of this review we found no new studies. There is no evidence from controlled trials to support or refute the use of any of the proposed interventions compared with radiotherapy. Therefore, the choice of intervention will be based on local resources. Radiotherapy techniques for managing vaginal bleeding are not readily available in resource-poor settings, where advanced cases of cervical cancer are predominant. Thus, this systematic review identified the need for a randomised controlled trial assessing the benefits and risks of palliative treatments for vaginal bleeding in women with advanced cervical cancer.

PLAIN LANGUAGE SUMMARY

Do vaginal packing, tranexamic acid, interventional radiology or other interventions control vaginal bleeding in women with advanced cervical cancer?

Background: cervical cancer (cancer of the neck of the womb) is the fourth most common cancer among women throughout the world, accounting for about 569,847 new detected cases and 311,365 deaths every year. Women more commonly present with advanced disease in the developing (low-income) world, where access to cervical screening programmes is limited. Advanced cancer of the cervix may not be curable and women often need treatment to control distressing symptoms (palliation), such as vaginal bleeding. Bleeding can be severe enough to be life threatening in women with advanced cervical cancer. Management of vaginal bleeding often poses a challenge, especially in the developing world, where access to radiotherapy is limited. Options for palliative treatment of severe vaginal bleeding include interventional radiology treatment (using x-rays to guide the insertion of 'plugs' into blood vessels supplying the cancer) or vaginal packing (where gauze is compacted into the vagina to absorb the blood and apply pressure directly to the cervix), although these are often only partly effective and may cause harm. Vaginal packs can be soaked with formalin, which is a preservative chemical. Other options for treating severe vaginal bleeding include tranexamic acid (a medicine that reduces bleeding that can be given by mouth or by injection) and radiotherapy (high-energy x-ray treatment).

Review question: the aim of this review was to compare tranexamic acid, vaginal packing (with or without formalin-soaked packs), interventional radiology or other interventions versus radiotherapy treatment to control vaginal bleeding in cervical cancer.

Main findings: the searches were updated to March 2018. We found no randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) for inclusion, so there is an absence of evidence that tranexamic acid, vaginal packing (with or without formalin-soaked packs), interventional radiology techniques or other interventions are as effective or safe as radiotherapy for palliative control of bleeding from the vagina in advanced cervical cancer. There is a need for randomised controlled trials or good-quality non-randomised comparative studies to determine the effectiveness and safety of these interventions when compared with radiotherapy in terms of symptom control, quality of life and side events.

Certainty of the evidence: no studies fulfilled the inclusion criteria and so there is no good-certainty evidence.

BACKGROUND

Description of the condition

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (2015, Issue 5) on palliative interventions for controlling vaginal bleeding in advanced cervical cancer (Eleje 2015). According to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, cervical cancer ranks fourth for both incidence and mortality of cancer among women worldwide, with only breast cancer, colorectal and lung cancer occurring more frequently (Bhatla 2019; Bray 2018; Ferlay 2019). Worldwide, cervical cancer accounts for estimated 569,847 new diagnoses and 311,365 deaths every year (Bray 2018; Ferlay 2019). Of the new cases, more than 85% occur in low- to middle-income countries, and in some of these countries cervical cancer is the most common cancer in women (Ikechebelu 2010; Obiechina 2009; Sankaranarayanan 2008). Therefore, nearly 70% of the global burden occurs in the developing world and more than one-fifth of all new cases are diagnosed in India (GLOBOCAN 2012). The highest regional incidence and mortality rates are seen in Africa, while in relative terms, the rates are 7 to 10 times lower in North America, Australia and New Zealand, and Western Asia (Bray 2018; Ferlay 2019).

Differences are largely affected by the availability of cervical screening. Studies in low- to middle-income countries continue to show a low to moderate level of awareness and utilisation of cervical cancer screening services (Ajayi 1998; Asonganyi 2013; Ayinde 2004; Bradford 2013; Bukar 2012; Gamaoun 2018; Hyacinth 2012; Mukakalisa 2014). This lack of effective screening also explains why in low- to middle-income countries over 75% of affected women present with an advanced stage, whereas in high-income countries over 75% of affected women present with early-stage disease (Ikechebelu 2010; NHSCSP 2007-2010; Umezulike 2007). Despite advances in cervical cancer prevention and diagnosis, outcomes for patients given a diagnosis of advanced and recurrent or metastatic disease are poor, with 5-year survival rates between 5% and 15% for such cases, and treatment options are very limited (Godoy-Ortiz 2018; Rosen 2017). Older women, who are at risk for a poorer overall prognosis because of their age, often do not receive the appropriate treatment and are also dying more frequently because of advanced cervical cancer (Quinn 2019).

Early-stage cancer of the cervix (stage I to IIa; Appendix 1), can be successfully treated by radical surgery (with or without neoadjuvant chemotherapy) or concomitant chemoradiation (FIGO Committee on Gynecologic Oncology 2014; Pecorelli 2009). For advanced cervical cancer (stages IIb to IVb; Appendix 1), the treatment is chemoradiotherapy or palliative chemotherapy with or without radiotherapy (Scatchard 2012). Women with advanced cancer of the cervix often need palliation for distressing symptoms, such as vaginal bleeding. In previous studies, the prevalence of vaginal bleeding in women with advanced cervical cancer ranged from 0.7% to 100% (Adewuyi 2008; Ikechebelu 2010; Shapley 2006; Tarney 2014; Umezulike 2007). Vaginal bleeding is the immediate cause of death in 6% of women with cervical cancer and its management often poses a challenge (Yennurajalingam 2009).

Description of the intervention

Due to the geographical differences in incidence, and with increased rates in low- to middle-income countries, there is a need for different palliative options to treat vaginal bleeding across a variety of healthcare settings. These include: vaginal packing; use of formalin-soaked vaginal packs; QuikClot combat gauze (Vilardo 2017); cautery; endoscopic haemostatic forceps (Kobara 2015); tranexamic acid; interventional radiology techniques, such as uterine artery embolisation; uterine artery resection; uterine artery ligation and ionising radiation/radiotherapy (Barbera 2010; Fletcher 2002; Pereira 2004; Seider 1988). Potentially helpful radiotherapy approaches include transvaginal orthovoltage treatment (cervical cone irradiation), high-dose fraction external beam radiotherapy or brachytherapy (irradiation delivered directly into the cervix/vagina). The type and length of treatment will depend on the woman's Karnofsky performance status (a standard way of measuring the ability of people with cancer to perform ordinary tasks). In a woman with a reasonable performance status, stereotactic radiosurgery may be considered to control bleeding (Konski 2005). In cases of uncontrollable bleeding, uterine artery embolisation may be required. This is a procedure performed using x-ray imaging for guidance to block feeding blood vessels to the uterus and cervix with metal coils, foam or glue-like agents. If radiographically directed embolisation is not available, laparotomy with ligation of uterine arteries or anterior divisions of the hypogastric arteries is an alternative, but is likely to be inappropriate in a palliative setting. However, a very few, well-selected women may derive benefit. Symptomatic anaemia resulting from blood loss can be remedied with blood transfusions once bleeding is stopped (Barbera 2010; Konski 2005).

Since there is no way to guarantee access to immediate radiotherapy in low- to middle-income countries, the use of formalin-soaked packs has been advocated for the treatment of haemorrhage associated with vaginal bleeding. Other vaginal packing procedures include the use of gauze (Vilardo 2017), lamb's wool or calcium alginate. Monsel's solution (i.e. ferric subsulphate) can also be used to stop vaginal bleeding from cervical cancer (Konski 2005).

Tranexamic acid can be given as an oral tablet or by injection to help to stabilise blood clots and stop bleeding by preventing fibrin degradation. It is effective in controlling blood loss in trauma situations and has been used to prevent blood loss during major surgery (CRASH-2 Collaborators 2011; Hunt 2015; Ker 2014; Ng 2015).

How the intervention might work

Cervical cancer tends to spread locally before it metastases to distant organs. When the cancer is confined to the pelvis or regional lymph nodes cure is possible with radical hysterectomy, chemoradiotherapy or a combination of the two. In the presence of distant metastatic disease, cervical cancer is generally not curable and treatment is given with palliative intent. In low- to middle-income countries, many women with cancer of the cervix present when the disease is already advanced and metastatic. At this stage, a degree of vaginal bleeding is almost inevitable. If there are distant metastases, there would be limited justification for embarking on aggressive surgical interventions such as bilateral ligation of the hypogastric arteries and so conservative approaches, such as packing of the vagina, use of haemostatic agents and palliative radiotherapy, are more appropriate (Konski 2005).

Oral or intravenous administration of tranexamic acid, three or four times per day, may be used to control/palliate mild-to-moderate vaginal bleeding. Tranexamic acid can have both direct and indirect actions. It antagonises the activation of plasminogen (mechanism for dissolving blood clots after they have been formed) by fastening to its kringle enzymatic domain (autonomous protein domains that fold into large loops, which are important in protein-protein interactions with blood coagulation factors). With this action, it reduces the conversion of plasminogen to plasmin. The inhibition of the formation of plasmin is important in controlling vaginal bleeding. In fibrinolysis (fibrin-splitting), plasmin breaks up the fibrin in blood clots, fibrinogen and other proteins in the blood plasma, such as procoagulant factors V and VIII. In addition, tranexamic acid can antagonise the actions of plasmin directly, though a higher dosage is required to achieve this action than the dosage required to inhibit its action on plasminogen. As well as approaches used to palliate vaginal bleeding, the volume of blood loss needs to be replenished adequately, using plasma expanders or packed red blood cells (CRASH-2 Collaborators 2011; Mishra 2011).

Tight vaginal packing with simple gauze rolls is a simple first-aid measure to control haemorrhage. For vaginal packing to be effective, the lithotomy position (legs up in stirrups) is ideal, with the use of an instrument (speculum) to expose the superior part of the vagina aseptically. Sedation or short-lasting general anaesthesia may be needed. The fornices of the vagina are tightly packed with the aim of maintaining an even pressure in the vagina. While the pack is in situ, the woman requires catheterisation, as she is likely to have difficulty in passing urine, due to compression on the urethra. Other simple measures, such as restricting that woman's mobility, foot-end elevation of the bed or haemostatic agents (local, oral or parenteral), may enhance the effectiveness of the vaginal packing (Mishra 2011). As long as the vaginal pack is present, broad-spectrum antibiotics, including metronidazole, may be helpful for treating any underlying infection, which is common with necrotic tumours and can contribute to haemorrhage.

Formalin also acts as a haemostatic agent by initiating a chemical cauterisation, reducing haemorrhage arising from small blood vessels (Chattopadhyay 2010; Vyas 2006). Formalin is an aqueous solution of the chemical compound formaldehyde. The formaldehyde in formalin is responsible for its cauterising property, while the water helps to dilute it, making the solution safer to use. A 4% solution of formalin has no toxic adverse effects (Vyas 2006). This concentration is well tolerated by women, and can help to control vaginal bleeding. Formalin contains noxythiolin (oxymethylenethiourea), tauroline (a condensate of two molecules of the aminosulponic acid taurine with three molecules of formaldehyde), hexamine (hexamethylenetetramine, methenamine), the resins melamine and urea formaldehydes, and imidazolone derivatives such as dantoin. These agents are claimed to be microbicidal, on account of the release of formaldehyde, as well as having some coagulase properties that allow the arrest of bleeding (Adebamowo 2000; Chattopadhyay 2010; Fletcher 2002).

Palliative-dose radiotherapy can be an effective treatment of vaginal bleeding in cancer of the cervix. The standard curative treatment fraction of radiotherapy is 1.8 Gy to 2.0 Gy in a single fraction. In palliative care, enhanced doses are given with fewer fractions (Mishra 2011).

When vaginal packing fails and radiotherapy is not feasible or available, measures aimed at decreasing the pulse pressure of the blood vessels feeding the cervical tumour can be implemented. These approaches largely comprise surgical interventions or interventional radiology procedures. However, in advanced disease there is often extensive neovascularisation from a variety of feeding vessels, limiting the utility of this approach. Therefore, for meaningful benefit, appropriate patient selection is essential. If excessive bleeding occurs in an end-of-life situation, anxiolytics and analgesics to relieve discomfort and distress are important palliative measures, as is psychological and supportive care of the woman and her relatives (Barbera 2010; Mishra 2011).

Mohs' paste works by releasing zinc ions when in contact with a cervical cancer tumour (Yanazume 2013a). Following contact, it precipitates wound proteins to aid haemostasis. These wound proteins include fibrin sealants, thrombin and platelet gels that provide activity during the augmentation or propagation, or both, phase of haemostasis (Glick 2013).

Monsel's solution (ferric subsulphate) is a haemostatic agent that can be applied directly to the bleeding cervix (Davis 1984; Jetmore 1993; Manca 1997; Ratliff 1992; Soyle 1992; Spitzer 1996). It can also be applied in addition to a gauze pack. It works by coagulating proteins, leading to tissue necrosis and eschar formation, enhancing thrombus formation and haemostasis (Glick 2013).

Platinum-based chemotherapy works by slowing down cancer cell growth and can improve survival and quality of life in advanced disease, with relatively minimal toxicity (Scatchard 2012). However, in cancers, new feeding blood vessels may be abnormal and inadequate leading to lower perfusion of the cancer cells. This may result in a reduced concentration of cytotoxic agents within the

tumour. The resulting hypoxia from poor blood supply may lower the proliferating fraction of cancer and reduce the potential cytotoxic effects of platinum-based chemotherapeutic agents (Lorusso 2014).

Bilateral ligation of the internal iliac arteries (main arteries feeding the pelvis) may work to control intractable bleeding from advanced cervical cancer, especially when vaginal tamponade and blood transfusion are ineffective (Gassibe 1997). However, this requires major surgery and general anaesthetic, which may not be appropriate in a palliative setting.

Endoscopic haemostatic forceps work by soft coagulation which is non-invasive (Kobara 2015), while QuikClot combat gauze is a synthetic haemostatic dressing used for haemorrhage control (Vilardo 2017).

One further supportive treatment is vitamin K. Vitamin K is essential for the hepatic (liver) production of a number of clotting factors, including factors II, VII, IX and X. Vitamin K treatment may be helpful if there is bleeding in the presence of a derangement of these factors or excessive warfarin therapy (which acts by inhibiting vitamin K-dependent clotting factor production by the liver) in women with advanced cancer (Shafi 2012).

Why it is important to do this review

Palliative measures to control bleeding in women with advanced cervical cancer are often needed (Barbera 2010; Fletcher 2002; Konski 2005). The intervention chosen is likely to be dependent on the severity of bleeding, but should also take account of effectiveness and the woman's wishes, and those of her family, especially in a palliative or potentially terminal care setting. Radiotherapy may not be suitable (if previously used in the treatment pathway) or may not be readily available, due to limitations in the healthcare setting. However, although there are benefits of non-invasive or minimally invasive palliative interventions, as compared with more invasive interventions, vaginal packing (non-invasive intervention) can be painful and distressing and may require sedation or general anaesthesia, whereas other simple measures, such as tranexamic acid, can also have harms associated with them.

There is currently no systematic review that addresses palliative interventions for controlling vaginal bleeding caused by advanced cervical cancer. Systematic reviews on the use of ionising radiation for controlling bleeding show that it can be associated with serious adverse consequences, such as bowel toxicity (Green 2005; Symonds 2004). This damage causes symptoms such as diarrhoea, mucous discharge, cramping, bloating, tenesmus and anal pain or incontinence (Luna-Pérez 2002). Vaginal bleeding remains a common consequence of advanced cervical cancer. Knowledge of the effectiveness of the interventions to reduce vaginal bleeding in women with advanced cervical cancer is essential to enable evidence-based clinical decisions. A systematic evaluation of other alternative palliative interventions is therefore warranted to inform decision-making for this important and distressing health need.

OBJECTIVES

To evaluate the efficacy and safety of tranexamic acid, vaginal packing (with or without formalin-soaked packs), interventional radiology or other interventions compared with radiotherapy for palliative treatment of vaginal bleeding in women with advanced cervical cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs) or controlled clinical trials (CCTs). We only included non-RCTs that used sensible statistical adjustment in the analysis to reduce the risk of selection bias, especially as women unfit for radiotherapy are given the alternative interventions. This was irrespective of publication status, year of publication or language.

Types of participants

Women (aged 18 years and over) with vaginal bleeding caused by advanced cervical cancer with or without metastasis. We included women with advanced cervical cancer in a palliative setting.

Types of interventions

Vaginal packing (with or without formalin-soaked packs), tranexamic acid, interventional radiology or other interventions compared with a control group who received radiotherapy.

Types of outcome measures

Primary outcomes

- Deaths from haemorrhage.
- Anaemia (defined as haemoglobin concentration less than 11 g/dL).

Secondary outcomes

- Time to next episode of recurrent vaginal bleeding.
- Need for subsequent radiotherapy to control bleeding.
- Need for blood transfusion.
- Vaginal itching/irritation.
- Deaths occurring during follow-up.
- Serious adverse events (life threatening, resulting in admission to hospital or discontinuation of treatment).

- Haematological and biochemical adverse effects (e.g. neutropenia, liver toxicity).
- Vomiting.
- Anaphylactoid reactions (e.g. dyspnoea, chest tightness, facial flushing, nausea, cyanosis, loss of consciousness, hypotension and death).
- Other adverse events, including venous thromboembolism and convulsion.

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases up to 21 March 2018:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 3) in the Cochrane Library (Appendix 2);
- MEDLINE via Ovid (March 2015 to March week 2, 2018) (Appendix 3);
- Embase via Ovid (March 2015 to week 12, 2018) (Appendix 4).

We sought reports in all languages and carried out translations when necessary. We attempted to identify unpublished studies.

Searching other resources

Grey literature

We searched metaRegister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, and www.cancer.gov/clinicaltrials for ongoing trials.

Handsearching

We handsearched the following journals from 1980.

- *African Health Sciences.*
- *African Journal of Biomedical Research.*
- *African Journal of Clinical and Experimental Microbiology.*
- *African Journal of Health Sciences.*
- *African Journal of Traditional, Complementary and Alternative Medicines.*
- *Alexandria Journal of Medicine.*
- *Benin Journal of Postgraduate Medicine.*
- *Clinics in Mother and Child Health.*
- *Continuing Medical Education.*
- *Global Journal of Medical Sciences.*
- *International Journal of Health Research.*
- *Journal of Biomedical Investigation.*
- *Journal of College of Medicine.*
- *Journal of Ethiopian Medical Practice.*
- *Journal of Medical Investigation and Practice.*
- *Journal of Medical Laboratory Science.*
- *Journal of Medicine and Biomedical Research.*
- *Journal of Medicine and Medical Sciences.*
- *Journal of Medicine in the Tropics.*
- *Journal of Pharmaceutical and Allied Sciences.*
- *Journal of Phytomedicine and Therapeutics.*
- *Journal of the Eritrean Medical Association.*
- *Libyan Journal of Medicine.*
- *Malawi Medical Journal.*
- *Mary Slessor Journal of Medicine.*
- *Medical Journal of Zambia.*
- *Nigerian Journal of Parasitology.*
- *Obstetrics and Gynaecology Forum.*
- *Orient Journal of Medicine.*
- *Port Harcourt Medical Journal.*
- *Journal of Orthomolecular Medicine.*

We also searched the following conference proceedings.

- American Congress of Obstetrics and Gynaecology.
- British International Congress of Obstetrics and Gynaecology.
- British Infection Association conference.
- Annual Meeting of the International Gynecologic Cancer Society.
- International Federation of Gynaecology and Obstetrics (FIGO).

Data collection and analysis

Two review authors (GE and AE) independently assessed for inclusion all the potential studies identified from the literature search. We resolved any disagreement through discussion or, if required, we consulted a third review author (GI). If we were uncertain about potential duplicate studies, we corresponded with the authors of the reports. We grouped multiple reports of the same study.

We examined the titles and abstracts to remove obviously irrelevant reports. We retrieved the full text of any potentially relevant reports. We examined the full-text reports for compliance of the studies with our eligibility criteria. We recorded the reasons for exclusion of studies.

We identified no studies suitable for inclusion in the review.

RESULTS

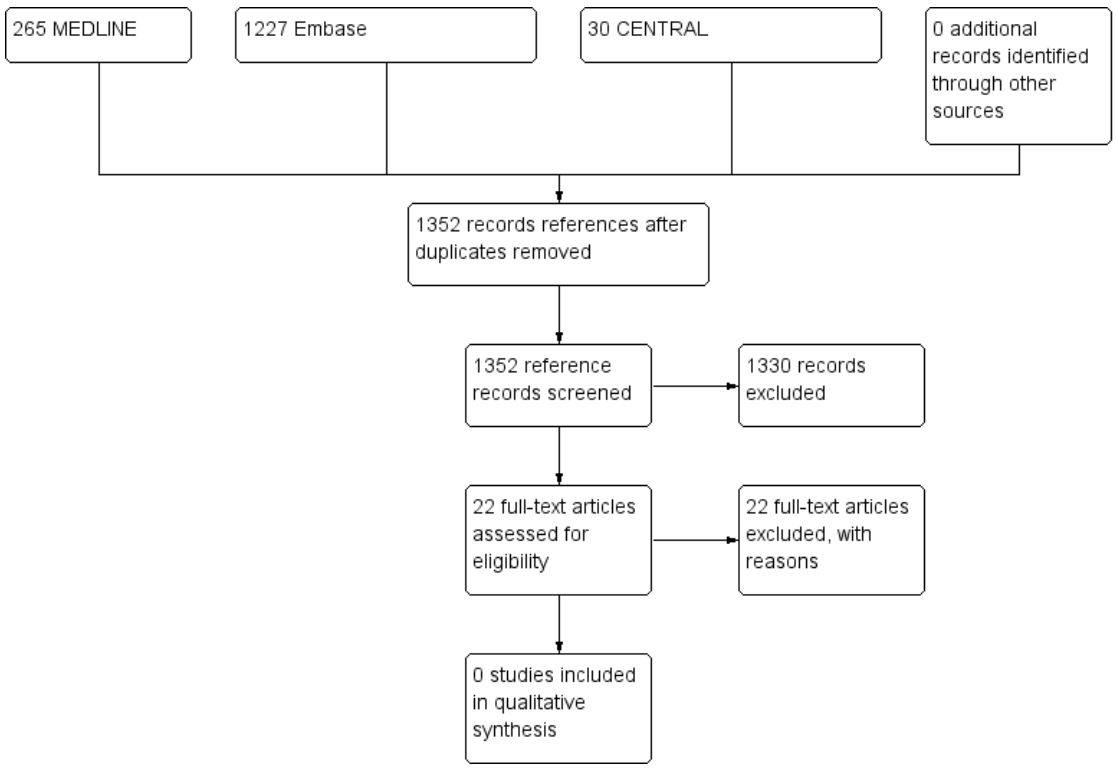
Description of studies

We identified no studies eligible for inclusion in the review. The studies listed in the Characteristics of excluded studies table were excluded because they were neither randomised trials nor comparative observational studies.

Results of the search

See Prisma flow diagram (Figure 1).

Figure 1. Study flow diagram.



The search strategy identified 1522 references (CENTRAL 30, MEDLINE 265 and Embase 1227). When the search results were merged into Endnote and duplicates removed, there were 1352 unique references. Two reviews authors (GU and AE) independently read the abstracts and articles and excluded 1330 records which did not meet the inclusion criteria. We retrieved 22 full-text articles and excluded all of the studies for the reasons described below (Excluded studies) and in the Characteristics of excluded studies table. Two review authors (GU and GI) independently searched the grey literature; we found no relevant studies.

Included studies

No studies met our inclusion criteria.

Excluded studies

We excluded 22 studies after obtaining the full-text papers for the following reasons.

- Six references were single-arm (without a comparison group) studies on the use of the intervention radiology in the control of vaginal bleeding in cervical cancer (Banaschak 1985;

Ermolov 2003; Ishikawa 1986; Kramer 1999; Mihmanli 2001; Yamashita 1994).

- Six references were single-arm (without a comparison group) studies on the use of the palliative radiotherapy in the control of vaginal bleeding in cervical cancer (Biswal 1995; Grigsby 2002; Kim 2013; Kraiphibul 1993; Mishra 2005; Onsrud 2001).
- One study was presented as a poster abstract at the European Cancer Congress in 2013 in Amsterdam, The Netherlands (Ahmedov 2013). The abstract was a single-arm (without a comparison group) study that involved the selective embolisation and chemoembolisation (using doxorubicin) of the anterior branch of the internal iliac artery performed on 78 women with cervical cancer.
- Two studies were case series on the application of formaldehyde-soaked packs and selective arterial embolisation to stop intractable vaginal bleeding in five women (Fletcher 2002), and three women (Zeghal 2013). None of the women in Fletcher 2002 had cervical cancer.
- Three references were descriptive reviews that mainly discussed palliative radiotherapy (Konski 2005; Skliarenko 2012), and general treatment options (Pereira 2004), for women with advanced cervical cancer.
- One study was a single-arm (without a comparison group) study involving the use of chemotherapy in women with cervical cancer (Adewuyi 2010).
- One study was a single-arm (without a comparison group) study on the use of extraperitoneal ligation of the hypogastric arteries in the control of vaginal bleeding in women with cervical cancer (Kwawukume 1996).
- One study was a single-arm (without comparison group) study on the use of Mohs' paste to achieved complete haemostasis within a single application in women with cervical cancer (Yanazume 2013a).
- One study was a short communication on the use of Monsel's solution in controlling vaginal bleeding in cervical cancer (Ratliff 1992).

None of the excluded studies reported on tranexamic acid, which is one of the interventions in the inclusion criteria for this review. For further details of all the excluded studies, see the Characteristics of excluded studies table.

Risk of bias in included studies

No studies met the inclusion criteria.

Effects of interventions

We identified no studies eligible for inclusion in this review. However, we did report results in a narrative discussion in the Agreements and disagreements with other studies or reviews section. These were single-arm, observational studies and were at a high risk of bias, although we did not objectively assess this, since they did not meet the inclusion criteria.

DISCUSSION

Summary of main results

We identified no studies that evaluated the efficacy and safety of tranexamic acid, vaginal packing (with or without formalin-soaked packs) or interventional radiology techniques when compared with radiotherapy for palliative treatment of vaginal bleeding in women with cervical cancer. The motivation behind this review was that in low- to middle-income countries, many women with advanced cervical cancers do not have access to radiotherapy treatment for the control of vaginal bleeding. This is because there are few hospitals with radiotherapy centres and those hospitals that do may not be functional due to operative logistics. This makes the use of alternative effective interventions for the control of vaginal bleeding extremely important.

Where a radiotherapy treatment service is available in low- to middle-income countries, many women may not be able to access it due to poverty. Most of the healthcare services available are situated in urban areas and far from the most vulnerable women. The referral system in most of the low-income countries is generally poor, for reasons including poor road networks, transport infrastructure and a lack of ambulance services. Where radiotherapy services are available, the number of women requiring radiotherapy for all malignancies may be far beyond the capacity of the facilities and expertise available, leading to prolonged waiting times and disease progression. Some cervical tumours are locally advanced at diagnosis and may cause profound haemorrhage, resulting in hypovolaemia and hypotension requiring immediate intervention and blood transfusion when histology results may not be available. Therefore, without histological confirmation in emergency cases, other alternative interventions to radiotherapy are essential to control vaginal bleeding. However, not all women requiring effective treatments for haemorrhage are in a resource-poor setting and so effective treatments for women in an emergency situation or in whom radiotherapy is no longer indicated (due to previous high-dose pelvic radiotherapy) are still needed.

Overall completeness and applicability of evidence

We identified no studies eligible for inclusion in this review. However, eligible studies could feasibly be conducted, but would be challenging. The challenge can arise from the difficulty in withholding radiotherapy when available for other non-radiotherapy interventions, which may appear less effective for the control of

bleeding and hence ethically difficult. However, studies could compare different initial treatment options, with palliative radiotherapy held in reserve if the initial treatment was ineffective. The following question remains unanswered: whether tranexamic acid, vaginal packing (with or without formalin-soaked packs) or interventional radiology techniques are safe and effective when compared with palliative radiotherapy for preventing vaginal bleeding in women with cervical cancer. Although, single-arm observational studies have shown a potential benefit for the control of vaginal bleeding, using vaginal packing with formalin-soaked packs or interventional radiology techniques, no definite judgement can be made.

Quality of the evidence

No studies fulfilled the inclusion criteria. Single-arm, non-comparator studies formed the only available evidence, but these study designs are at significant risk of bias. Non-randomised studies are unlikely to address the objectives of the review adequately and, unless well-designed and adjusted for sensible covariates, are likely to be at high risk of bias and the overall quality of the evidence is likely to remain very low.

Potential biases in the review process

In order to prevent bias in the review process, the Cochrane Gynaecological Cancer Review Group developed and conducted the search. We performed a comprehensive search, including a thorough search of the grey literature and two review authors independently sifted and assessed all studies. We were not restrictive in our inclusion criteria with regards to types of studies as we planned to include good-quality non-randomised studies and, we attempted not to overlook any relevant evidence by searching a wide range of quality non-randomised study designs.

Potentially, the greatest threat affecting the validity of the review is likely to be publication bias. This is because some studies that may have found that vaginal packing alone was not effective in controlling vaginal bleeding and subsequently used the standard intervention such as radiotherapy may not have published it as a comparative study. We were unable to assess this possibility, as we found no studies that met the inclusion criteria.

Agreements and disagreements with other studies or reviews

Currently, there are no systematic reviews of palliative interventions for controlling vaginal bleeding in advanced cervical cancer. We found only one systematic review on palliative radiotherapy for cervical cancer (van Lonkhuijzen 2011), which reviewed optimal palliative radiation doses for the treatment of advanced cervical cancer (van Lonkhuijzen 2011). The review identified eight studies for potential inclusion and none compared the results of different fractionation schemes. Unlike the present review, the van Lonkhuijzen 2011 review did not primarily determine interventions for controlling vaginal bleeding in cervical cancer. Most of the excluded studies were observational retrospective studies, with significant risk of bias. No studies validated endpoints for symptom relief, such as vaginal bleeding, although some reported varying amounts of relief from vaginal bleeding. However, the documentation of acute and late toxicity of radiotherapy was poor (van Lonkhuijzen 2011). The authors concluded that there is a dearth of information to guide the selection of an optimal palliative radiation schedule for treatment of women with advanced cervical cancer, and no evidence to support the common belief that better and longer palliation is achieved with a high doses delivered in multiple, smaller fractions.

However, all the relevant, but excluded, studies appeared to have been designed as single-arm studies, aiming to assess whether formalin packs, radiotherapy or intervention radiology can be used effectively and in a palliative setting in cases of vaginal bleeding in women with cervical cancer. The study designs allowed no assessment and comparison of the effect of the various interventions on vaginal bleeding control.

For example, in single-arm studies on the use of radiotherapy in palliative interventions in vaginal bleeding in women with cervical cancers, the overall response rates in terms of control of vaginal bleeding ranged from 90% (Onsrud 2001) to 100% (Biswal 1995; Kraiphibul 1993; Mishra 2005). The treatment was generally well tolerated with a median survival of seven months (Mishra 2005). However, single-arm studies (without a comparison group) on the use of interventional radiology (embolisation of iliac or uterine arteries, or both), revealed that the overall response rate in terms of vaginal haemostasis was 70% (Kramer 1999), 93% (Grigsby 2002), and 100% (Ermolov 2003; Mihmanli 2001; Yamashita 1994; Zeghal 2013), though there was documented recurrence of bleeding after initially controlling the bleeding in all women (Yamashita 1994). Interventional radiology has relatively minor acute or long-term toxicity (Grigsby 2002). In two studies, there were no complications following embolisation therapy (Yanazume 2013a; Zeghal 2013), except for transient fever and lower abdominal pain (Yamashita 1994). Ermolov 2003 concluded that embolisation of uterine arteries is a safe and highly effective alternative to radical surgical interventions in women with acute gynaecological disease complicated by vaginal bleeding. Interventional radiology can provide effective haemostasis and permit either avoidance of surgical intervention or a significant reduction in the volume of intraoperative blood loss. Similarly, Mihmanli 2001 also concluded that transarterial embolisation is a life-saving procedure in treating intractable vaginal bleeding due to cervical cancer.

Other non-comparative studies have shown that paraformaldehyde-soaked vaginal packs could be beneficial (Fletcher 2002). In this intervention, the packs were kept in situ for approximately 24 hours and were removed when there was no further evidence of

bleeding. The woman responded well to the treatment and made a full recovery. There was no reported adverse effects (Fletcher 2002).

Mohs' paste achieved complete haemostasis with a single application in one case report (Yanazume 2013a). Haemostasis lasted for more than six months and the woman died of multiple organ failure without further vaginal bleeding (Yanazume 2013a). In another study involving Mohs' paste, eight women with extensive genital bleeding from the uterine cervix or vaginal stump, due to recurrent gynaecological cancer, had Mohs' paste applied directly to the bleeding tumour. The effect of Mohs' paste lasted for at least three months in three women and none of the eight women died of genital bleeding (Yanazume 2013b).

A vaginal pack soaked in Monsel's solution (ferric sulphate, sulphuric and nitric acids) aids haemostasis in women with vaginal bleeding due to cervical cancer (Ratliff 1992), although the majority of its use in the published literature is on premalignant lesions of the cervix (Attarbashi 2007; Tam 2005).

Of seven cases that had extraperitoneal ligation of the internal iliac arteries to control bleeding, five were from women with advanced cervical cancer in a report by Kwawukume 1996. Extraperitoneal ligation of the internal iliac arteries arrested haemorrhage, without the need for any further blood transfusion (Kwawukume 1996). Although the authors of Kwawukume 1996 described the performance of ligation of internal iliac artery abdominally or extraperitoneally, laparoscopic ligation of internal iliac artery has also been described in the published literature (Gassibe 1997; Skret 1994; Skret 1995; Sobiczewski 2002), and so laparoscopy appears to be an alternative procedure to abdominal or extraperitoneal ligation of internal iliac artery in vaginal bleeding due to cervical cancer.

In Adewuyi 2010, where 84/111 women had at least FIGO stage IIIA disease, 81 women had complete cessation of vaginal bleeding, with 69 women having complete cessation on or before the fourth course of cisplatin-based chemotherapy (ninth week). Adewuyi 2010 concluded that in low-resource settings, platinum-based chemotherapy can be used to control vaginal bleeding and improve the quality of life of women pending radiotherapy. Similar to Adewuyi 2010 study, Orang'o 2017 evaluated the effectiveness and feasibility of cisplatinum for palliative treatment of advanced cervical cancer in a resource-poor setting and concluded it was feasible and led to effective symptom control.

It is worth noting that all of these studies are likely to be at critical risk of bias.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review, we found no new studies eligible for inclusion. There is no evidence, as we found no comparative studies assessing vaginal packing with or without formaldehyde, tranexamic acid or interventional radiology compared with radiotherapy for women with vaginal bleeding due to advanced cervical cancer. Many non-comparative observational studies have reported high success rates on the use of these alternative palliative interventions to radiotherapy in the control of vaginal bleeding. However, these are likely to be at critical risk of bias. Clinicians should consider alternative palliative interventions, and counsel women adequately, especially on the challenges of their use in cervical cancer. This is because almost all of the women with advanced cervical cancer need radiotherapy and its use in low- and middle-income countries (LMICs) is limited. Despite LMICs being home to 85% of the world's population, less than 35% of the world's radiotherapy facilities are available in these areas (IAEA 2008; WHO 2011). This inequity goes even further when comparing the availability of radiotherapy services across subregions. This is because effective prevention, early detection and screening services are often also absent, hence, a higher proportion of cervical cancer in these countries is detected at an advanced stage, leaving palliative radiotherapy as one of the only options for treatment (Barton 2006). Thus, the triad of inequity of access, availability and affordability of radiotherapy treatment constitutes a major challenge for the implication of this review in practice, thereby increasing the reliability and desirability of other palliative interventions to improve the satisfactory quality of lives of women with bleeding due to cervical cancer.

In all resource settings, simple local measures, such as vaginal packing and oral haemostatic agents (e.g. tranexamic acid), should be considered prior to, or as an alternative to, more interventional approaches, such as radiotherapy or embolisation. General measures of supportive care should be carried out. The woman's wishes should be respected and distress for women and their families should be minimised.

Implications for research

Currently, there is an absence of evidence for the routine use of vaginal packing (with or without formaldehyde), tranexamic acid, interventional radiology or other interventions compared with radiotherapy in the control of vaginal bleeding in advanced cervical cancer. We encourage the development of clinical trials with random allocation of individual alternative interventions where radiotherapy is unavailable or not suitable due to previous treatment with radiotherapy. Future studies should look at alternatives to radiotherapy rather than a direct comparison with radiotherapy, since comparative randomised controlled trials are unlikely. This is because if radiotherapy is available, it would be used without comparison to other palliative interventions in a trial. However, often in emergency situations, these treatments remain options for consideration, perhaps used in a step-wise manner.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adewuyi 2010	Single-arm study (without a comparison group) involving the use of chemotherapy at a dose of 70 mg/m^2 every 3 weeks in women with cervical cancer. Chemotherapy was not part of review protocol intervention
Ahmedov 2013	Presented as a poster abstract at the European Cancer Congress in 2013 at Amsterdam, the Netherlands. The abstract was a single-arm (no comparison group) study that involved the selective embolisation and chemoembolisation (with doxorubicin) of anterior branch of internal iliac artery performed on 78 women with cervical cancer
Banaschak 1985	Case series of 12 women with acute massive or chronic tumour haemorrhage, treated with embolisation (without a comparison group) with only 10/12 women with cervical cancer, while 1 woman with progressive malignant mesenchymal tumour in the vagina and 1 with local persistent ovarian cancer
Biswal 1995	Single-arm (without comparison group) study of 20 women with refractory haemorrhagic carcinoma of the uterine cervix receiving haemostatic radiotherapy (external and intracavitary radiotherapy) between April 1987 and May 1992
Ermolov 2003	Single-arm (without comparison group) study involving the use of free Gianturco-type spirals for embolisation of internal iliac and uterine arteries in 24 women, out of which only 2 had cervical cancer
Fletcher 2002	Case series involving the application of formaldehyde-soaked packs to stop intractable vaginal bleeding in 2 cases of gestational trophoblastic disease and primary postpartum haemorrhage due to vaginal laceration
Grigsby 2002	Single-arm (without comparison group) study on the use of the high-dose rate cervical ring applicator to control acute cervical bleeding from carcinoma of the uterine cervix in 15 women presenting with acute vaginal bleeding requiring blood transfusion
Ishikawa 1986	Single-arm (without comparison group) study of 6 women with severe vaginal bleeding treated with transcatheter embolisation of selected pelvic vessels with only 3 women having carcinoma of the cervix, 1 with dysfunctional uterine bleeding and 2 women had gestational trophoblastic disease with bleeding from vaginal metastases
Kim 2013	Single-arm (without comparison) retrospective study of 17 women with cancer of the cervix, who underwent palliative hypofractionated 3-dimensional conformal radiotherapy between January 2002 and June 2012, and were retrospectively analysed
Konski 2005	Review based on palliative radiotherapy.
Kraiphibul 1993	Single-arm (without comparison group) study of 35 women with massive vaginal bleeding due to carcinoma of the cervix treated via cobalt-60 teletherapy covering the whole pelvic region by 12 × 12 cm^2 or 16 × 16 cm^2 field sizes from 1 June 1981 to 31 May 1991.

(*Continued*)

Kramer 1999	Single-arm (without comparison group) study of 13 women with advanced cervical cancer treated with embolisation performed by transfemoral access using mini coils in most cases, liquid agents less often and a covered vascular stent in 1 woman
Kwawukume 1996	Single-arm (without comparison group) study of 7 cases of extraperitoneal ligation of the hypogastric arteries to control bleeding from advanced cervical cancer (in 5 cases) and choriocarcinoma (in 2 cases). Hypogastric artery ligation was not part of the review protocol intervention
Mihmanli 2001	Single-arm (without comparison group) study of 6 women, 4 with cervix carcinoma, 1 endometrium carcinoma and 1 vaginal metastasis of ovarian carcinoma who underwent percutaneous embolisation due to intractable vaginal bleeding using polyvinyl alcohol particles as the embolic agent
Mishra 2005	Single-arm (without comparison group) study of 100 women treated with parallel-opposed pelvic portals with megavoltage radiotherapy monthly up to a maximum of 3 fractions (10 Gy/fraction)
Onsrud 2001	Single-arm (without comparison group) study of the effects of single fractions of 10 Gy pelvic irradiation for palliation and life prolongation on 37 women with cervical cancer and 27 women with corpus cancer treated in 1988-1998
Pereira 2004	Review based on treatment options available to manage visible bleeding from advanced cancer
Ratliff 1992	Short communication based on preventing cervical bleeding with Monsel's solution in gynaecological oncology when bleeding from cervical and vaginal biopsies was difficult to control. Monsel's solution was not part of the review protocol intervention
Skliarenko 2012	Review based on palliative pelvic radiotherapy for gynaecological cancer
Yamashita 1994	Single-arm (without comparison group) study of 32 women; 15 with postpartum haemorrhage, 12 with primary cervical cancer and 5 other malignant neoplasms that underwent transcatheter arterial embolisation. Only 10 women underwent subsequent treatment with radiotherapy. Results were not compared with transcatheter arterial embolisation group
Yanazume 2013a	Case report of a 55-year-old, multiparous woman with massive genital bleeding despite prior 1-year concurrent chemoradiation (pelvic radiation and intracavitary radiation) for FIGO stage IIIb squamous cell carcinoma of the uterine cervix. She achieved complete haemostasis with a single application of Mohs' paste
Zeghal 2013	Case series involving the selective arterial embolisation in 3 cases of women having vaginal bleeding in advanced cervical cancer

APPENDICES

Appendix 1. FIGO (2018) staging for cervical cancer

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a].
IA1	Measured stromal invasion <3 mm in depth.
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth.
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b].
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension.
IB3	Invasive carcinoma ≥4 cm in greatest dimension.
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension.
IIA2	Invasive carcinoma ≥4 cm in greatest dimension.
IIB	With parametrial involvement but not up to the pelvic wall.
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c].
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations)[c].
IIIC1	Pelvic lymph node metastasis only.
IIIC2	Para-aortic lymph node metastasis.

(*Continued*)

IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs.
IVB	Spread to distant organs.
Footnotes	[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages. [b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered. [c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned Source:Bhatla 2019

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Formaldehyde] explode all trees
#2 (formalin or forma-ray or formadon or formalaz or formaldehyde or formalyde-10 or formic aldehyde or formol or lazerformalyde or methanal or methyl aldehyde or oxomethane or veracur)
#3 MeSH descriptor: [Embolization, Therapeutic] explode all trees
#4 (embolization or embolisation)
#5 MeSH descriptor: [Radiology, Interventional] this term only
#6 interventional radiology
#7 MeSH descriptor: [Radiotherapy] explode all trees
#8 (radiotherap* or irradiation or radiation)
#9 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#10 MeSH descriptor: [Tranexamic Acid] this term only
#11 (tranexamic acid or lysteda or transamin)
#12 (pack* or gauze*)
#13 MeSH descriptor: [Hemostatics] explode all trees
#14 hemostat*
#15 MeSH descriptor: [Palliative Care] this term only
#16 palliat*
#17 MeSH descriptor: [Ligation] this term only
#18 MeSH descriptor: [Cautery] explode all trees
#19 (ligat* or cauter* or resect*)
#20 MeSH descriptor: [Radiosurgery] this term only
#21 radiosurgery
#22 MeSH descriptor: [Ferric Compounds] explode all trees and with qualifier(s): [Therapeutic use - TU]
#23 (monsel* or ferric subsulfate)
#24 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 MeSH descriptor: [Uterine Hemorrhage] explode all trees
#26 ((vagina* or uter*) near/5 (bleed* or hemorrhag* or haemorrhag*))

#27 #25 or #26
#28 MeSH descriptor: [Uterine Cervical Neoplasms] this term only
#29 (cervi* near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma* or choriocarcinoma* or teratoma* or sarcoma*))
#30 #28 or #29
#31 #24 and #27 and #30

Appendix 3. MEDLINE search strategy

MEDLINE Ovid
1 exp Formaldehyde/
2 (formalin or forma-ray or formadon or formalaz or formaldehyde or formalyde-10 or formic aldehyde or formol or lazerformalyde or methanal or methyl aldehyde or oxomethane or veracur).mp.
3 exp Embolization, Therapeutic/
4 (embolization or embolisation).mp.
5 Radiology, Interventional/
6 interventional radiology.mp.
7 exp Radiotherapy/
8 (radiotherap* or irradiation or radiation).mp.
9 radiotherapy.fs.
10 Tranexamic Acid/
11 (tranexamic acid or lysteda or transamin).mp.
12 (pack* or gauze*).mp.
13 exp Hemostatics/
14 hemostat*.mp.
15 Palliative Care/
16 palliat*.mp.
17 ligation/
18 exp cautery/
19 (ligat* or cauter* or resect*).mp.
20 radiosurgery/
21 radiosurgery.mp.
22 exp ferric compounds/tu
23 (monsel* or ferric subsulfate).mp.
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 exp Uterine Hemorrhage/
26 ((vagina* or uter*) adj5 (bleed* or hemorrhag* or haemorrhag*)).mp.
27 25 or 26
28 uterine cervical neoplasms/
29 (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma* or choriocarcinoma* or teratoma* or sarcoma*)).mp.
30 28 or 29
31 24 and 27 and 30
key:
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix 4. Embase search strategy

Embase Ovid
1 formaldehyde/
2 (formalin or forma-ray or formadon or formalaz or formaldehyde or formalyde-10 or formic aldehyde or formol or lazerformalyde or methanal or methyl aldehyde or oxomethane or veracur).mp.
3 therapeutic embolization.ti.
4 (embolization or embolisation).mp.
5 interventional radiology/
6 interventional radiology.mp.
7 exp radiotherapy/
8 (radiotherap* or irradiation or radiation).mp.
9 rt.fs.
10 tranexamic acid/
11 (tranexamic acid or lysteda or transamin).mp.
12 (pack* or gauze*).mp.
13 exp hemostatic agent/
14 hemostat*.mp.
15 exp palliative therapy/
16 palliat*.mp.
17 exp ligation/
18 cauterization/
19 (ligat* or cauter* or resect*).mp.
20 exp radiosurgery/
21 radiosurgery.mp.
22 (monsel* or ferric subsulfate).mp.
23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 uterus bleeding/
25 ((vagina* or uter*) adj5 (bleed* or hemorrhag* or haemorrhag*)).mp.
26 24 or 25
27 exp uterine cervix tumor/
28 (cervi* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma* or choriocarcinoma* or teratoma* or sarcoma*)).mp.
29 27 or 28
30 23 and 26 and 29
key:
[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

WHAT'S NEW

Date	Event	Description
7 February 2019	New search has been performed	Text and searches updated.
7 February 2019	New citation required but conclusions have not changed	Searches updated but no new studies identified for inclusion

CONTRIBUTIONS OF AUTHORS

GE and AE conceived, designed and coordinated the review.

LE participated in designing the review.

All the authors participated in writing and providing general advice on the review. All the authors agreed on the final version.

GE and AE undertook the review update.

DECLARATIONS OF INTEREST

GE: none known.

AE: none known.

GI: none known.

AI: none known.

LE: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to make clear which comparison is of interest to serve as control in our objective of this review and type of intervention, we have removed "no treatment or placebo" as a comparator intervention as was originally seen in the protocol. We consider that by making this change, we have removed the ethical problems that may arise in carrying out the randomised controlled trial or controlled clinical trial since it will be unethical to withhold treatment or give placebo treatment in women with vaginal bleeding when standard or alternative interventions for the control of the vaginal bleeding are available. We changed the reference citation 'Symonds 2003' to Symonds 2004 as the previous citation was incorrect.

Although not part of the interventions in the protocol for this review, we included Mohs' paste, Monsel's solution, platinum-based chemotherapy and extraperitoneal ligation of the hypogastric arteries as interventions. This is because they provided haemostasis in bleeding cervical cancer in non-comparative studies (Adewuyi 2010; Kwawukume 1996; Ratliff 1992; Tangtrakul 1979; Yanazume 2013a). For example, the details of the effects and outcomes of these interventions have been described in the published non-comparative studies as shown in Agreements and disagreements with other studies or reviews.

In line with the above, we added/included the following under Description of the intervention.

Mohs' paste is a mixture of zinc chloride (50 g), distilled water (25 mL), zinc starch (19 g) and glycerol (15 mL), where zinc ions are produced from the tumour when in contact with the paste (Yanazume 2013a). Its use was pioneered early by Mohs in his use of Mohs' surgery (Mohs 1941). Following contact, it precipitates wound proteins to aid haemostasis.

Monsel's solution is a mixture of ferric sulphate, and sulphuric and nitric acids. It is often called a 20% ferric subsulphate solution (Glick 2013). Monsel's solution aids haemostasis in women with vaginal bleeding due to cervical cancer (Konski 2005; Ratliff 1992),

although the majority of its use in the published literature is on premalignant lesions of the cervix (Attarbashi 2007; Tam 2005). This can be effectively achieved using a vaginal pack soaked in Monsel's solution.

Cisplatin is a cytotoxic chemotherapy that is effective in the control of vaginal bleeding due to advanced cervical cancer (Adewuyi 2010). Unfortunately, toxicity is an issue of concern in a population in which the treatment remains palliative in the finality since most women with advanced cervical cancer will have impaired renal function and cisplatin is potentially nephrotoxic (Lorusso 2014).

Ligation of the hypogastric arteries (main arteries of the pelvis situated nearer the front of the body) could be a life-saving palliative procedure for women with intractable haemorrhage in advanced cervical cancer (Gassibe 1997; Kwawukume 1996; Papp 1989; Skret 1994; Skret 1995; Sobiczewski 2002). Laparoscopic procedure (Gassibe 1997; Skret 1994; Skret 1995; Sobiczewski 2002) is an alternative procedure to abdominal or extraperitoneal ligation (Kwawukume 1996; Papp 1989) of internal iliac artery in these cases of advanced cervical cancer. During the laparoscopic procedure, a Hulka clip could be used to collapse the artery walls (Gassibe 1997). The laparoscopic procedure is less traumatic than laparotomy or open surgery.

In addition, in line with the above, we added the following under How the intervention might work.

Mohs' paste works by releasing zinc ions when in contact with a cervical cancer tumour (Yanazume 2013a). Following contact, it precipitates wound proteins to aid haemostasis. These wound proteins include fibrin sealants, thrombin and platelet gels that provide activity during the augmentation or propagation, or both, phase of haemostasis (Glick 2013).

Monsel's solution (ferric subsulphate) is a haemostatic agent that can be applied directly to the area of cervix that is bleeding (Davis 1984; Jetmore 1993; Manca 1997; Ratliff 1992; Soyle 1992; Spitzer 1996). It can also be applied via a gauze pack. It works by coagulating proteins leading to tissue necrosis and eschar formation enhancing thrombus formation and haemostasis (Glick 2013).

Platinum-based chemotherapy works by slowing down cancer cell growth and can improve survival and quality of life in advanced disease, with relatively minimal toxicity (Scatchard 2012). However, in cancers, new feeding blood vessels may be abnormal and inadequate leading to lower perfusion of the cancer cells. This may result in a reduced concentration of cytotoxic agents within the tumour. The resulting hypoxia from poor blood supply may lower the proliferating fraction of cancer and reduce the potential cytotoxic effects of platinum-based chemotherapeutic agents (Lorusso 2014).

Bilateral ligation of the internal iliac arteries (main arteries feeding the pelvis) may work to control intractable bleeding from advanced cervical cancer, especially when vaginal tamponade and blood transfusion are ineffective in reducing haemorrhage (Gassibe 1997). This is because internal iliac artery constitute the largest blood supply to the uterus and cervix and its ligation will cut off the blood supply, hence achieving haemostasis.

One further supportive treatment is vitamin K. Vitamin K is essential for the hepatic (liver) production of a number of clotting factors, including factors II, VII, IX and X. Vitamin K treatment may be helpful if there is bleeding in the presence of a derangement of these factors or excessive warfarin therapy (which acts by inhibiting vitamin K-dependent clotting factor production by the liver) in women with advanced cancer (Shafi 2012).

Bilateral ligation of the hypogastric arteries (main arteries of the pelvis situated nearer the front of the body) works in the control of intractable bleeding from advanced cervical cancer especially when vaginal tamponade and blood transfusion are ineffective in stopping the haemorrhage (Gassibe 1997). This is because, internal iliac artery constitute the largest blood supply to the uterus and cervix and its ligation will cut off the blood supply, hence achieving haemostasis.

Types of outcome measures

In line with suggestion by the peer reviewers, we have included the following in the outcome measures.

Primary outcomes

- Deaths from haemorrhage.

Secondary outcomes

- Need for blood transfusion.
- Vaginal itching/irritation.
- Deaths occurring during follow-up.

- Serious adverse events (life threatening, resulting in admission to hospital or discontinuation of treatment).
- Haematological and biochemical adverse effects (e.g. neutropenia, liver toxicity).
- Vomiting.
- Anaphylactoid reactions (e.g. dyspnoea, chest tightness, facial flushing, nausea, cyanosis, loss of consciousness, hypotension and death).
- Other adverse events, including venous thromboembolism and convulsion.

Data extraction and management

We will design a form for the extraction of data from the included trials. The data to be extracted will include:

- study design, allocation sequence generation, allocation concealment, blinding of participants and other concerns about bias, including information on ethical approval;
- total number of participants and number allocated to each intervention group, diagnostic criteria, age, parity, the stage of the cervical cancer, previous treatment for cervical cancer, details of missing participants, participant details, FIGO stage details, grade of tumour, performance status;
- details of the intervention, including the duration of application (formalin) and the frequency of the application of the haemostatic dose of radiotherapy;
- outcome definitions and time point outcomes.

For eligible studies, two review authors (GE and AE) will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third review author (GI). We will enter data into the Review Manager 5 software (Review Manager 2011), and check the data for accuracy.

Assessment of risk of bias in included studies

Two review authors (GE and AE) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving a third review author (GI).

- **Random sequence generation (checking for possible selection bias)**

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will summarise the risk of bias for each important outcome within and across studies.

We will assess the method as:

  - low risk of bias for participants and personnel (any truly random process, e.g. random number table; computer random number generator);
  - high risk of bias for participants and personnel (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
  - unclear risk of bias for participants and personnel.

- **Allocation concealment (checking for possible selection bias)**

We will describe for each included study the method used to conceal allocation to the interventions prior to assignment and assess whether the allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We will assess the methods as:

  - low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
  - high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternate allocation; date of birth);
  - unclear risk of bias.

- **Blinding of participants and personnel (checking for possible performance bias)**

We will describe for each included study the methods used, if any, to blind study participants and personnel to knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect the results.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

- **Blinding of outcome assessment (checking for possible detection bias)**

We will describe for each included study the methods used, if any, to blind outcome assessors to knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

- **Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)**

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data, including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will include missing data in the analyses that we undertake. We will assess methods as:

- low risk of bias (e.g. no missing outcome data; less than 20% missing outcome data; numbers and reasons for dropouts and withdrawals in all intervention groups were described; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data not balanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

- **Selective reporting (checking for reporting bias)**

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study failed to include results for a key outcome that would have been expected to have been reported);
- unclear risk of bias.

- **Other bias (checking for bias due to problems not covered by the above)**

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

- **Overall risk of bias**

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to selection, performance, detection, attrition, reporting and other biases above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratios with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured using the same scale between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods (e.g. time-to-event data, log hazard ratios and their standard errors, or where not available directly, data that will enable the estimation of log hazard ratios and their standard errors).

Unit of analysis issues

Multi-arm trials

If we identify any multi-arm trials, we will include these if any pair-wise comparisons of the intervention groups are relevant to the review and meet our inclusion criteria. We will report all the intervention groups involved in the study in the 'Characteristics of included studies' table, but we will include only those intervention groups relevant to the review in the analysis. We will address pair-wise comparisons in multi-arm trials in relevant meta-analyses if they are eligible for the analysis, and we will ensure that data from any one participant are included only once when pooling data. If there are multiple intervention groups in a particular study, we will combine all relevant experimental intervention groups of the study into a single intervention group and combine all relevant control intervention groups into a single control group (Higgins 2011). For example, there may be multiple treatment attempts and so the outcome will be regarded as recurrence and be included as such. We will handle events that may reoccur (such as bleeding) as recurrence of the outcome. We will handle time to event data (e.g. overall survival and time to next episode of vaginal bleeding). We will ensure that count data are not treated as dichotomous data. We will identify cluster-randomised trials, if any, and include them in the analysis.

Cross-over trials

We consider cross-over designs inappropriate for this research question.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, that is, we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing. We will contact the original investigators to request missing data. We will not impute missing standard deviations. We will not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T and I^2 statistics and the Chi^2 test (Higgins 2011). If there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, we will not carry out a meta-analysis.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate small-study effects using funnel plots. We will assess funnel plot asymmetry visually and use formal tests. For continuous outcomes, we will use the test proposed by Egger 1997, and for dichotomous outcomes, we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will investigate possible sources of funnel plot asymmetry, such as publication bias, location bias, selective outcome reporting and poor methodological quality.

Data synthesis

We will use a random-effects meta-analysis to incorporate heterogeneity among studies, primarily for heterogeneity that cannot be explained. We will carry out statistical analysis using the Review Manager 5 software (Review Manager 2011).
If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if a mean treatment effect across trials is considered clinically meaningful.
We will treat the random-effects summary as the mean range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the mean treatment effect is not clinically meaningful, we will not combine trials.

- For dichotomous outcomes, we will use the DerSimonian and Laird method to combine study results.
- For continuous outcomes, we will use the inverse-variance method.
- For time-to-event outcomes, we will use the generic inverse variance method to pool study results.

Subgroup analysis

If we identify substantial heterogeneity, we will investigate it using subgroup analyses. We will consider whether an overall summary is meaningful and, if it is, use a random-effects analysis to produce it. We will conduct subgroup analysis if there is an adequate number of studies.
We plan to carry out the following subgroup analyses.

- Parity: nulliparous versus multiparous women.
- Duration of application of formalin (less than one hour versus more than one hour).
- Frequency of application of haemostatic dose of radiotherapy (one versus more than one).
- Stage of cervical cancer.
- Previous treatment for cervical cancer.

Subgroup analysis will be restricted to the primary outcomes.

Sensitivity analysis

We will carry out sensitivity analysis to explore the effects of trial quality (assessed based on allocation concealment and other risk of bias components) by omitting studies rated as 'high risk of bias' for these components. We will restrict this to the primary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifibrinolytic Agents [therapeutic use]; Palliative Care [*methods]; Tampons, Surgical; Tranexamic Acid [therapeutic use]; Uterine Cervical Neoplasms [*complications; pathology]; Uterine Hemorrhage [etiology; *therapy]

MeSH check words

Female; Humans