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Review Article

PAIN

Epidural blood patch for post-dural puncture headaches in adult and paediatric patients with malignancies: a review

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Summary

Many anaesthetists are hesitant to perform epidural blood patch in patients with cancer because of the potential risk of seeding the CNS with malignant cells. Recent evidence suggests that anaesthetists may view malignancy as a *relative* contraindication to epidural blood patch rather than an *absolute* contraindication. This review article summarises the clinical dilemma, reviews the existing literature, and proposes a treatment algorithm that includes the utilisation of for the management of post-dural puncture headache in the oncology population.

Keywords: epidural blood patch; headache; lumbar puncture; oncology; pain management; post-dural puncture headache

Editor's key points

- Patients with oncological diagnoses are prone to post-dural puncture headaches given the need for repeated lumbar punctures.
- Anaesthetists have been hesitant to perform epidural blood patch in these patients given the risk of seeding the neuraxis with malignant cells.
- Recent literature shows the safe and effective use of epidural blood patching in the oncology population, with no documented cases of neuraxial seeding.
- This review article summarises the existing literature regarding epidural blood patch use in the oncology population and suggests a treatment algorithm for approaching this complex clinical dilemma.

Post-dural puncture headaches (PDPHs) occur in 10–40% of patients receiving diagnostic lumbar punctures (LPs) and can have significant clinical consequences.[1] Most cases of PDPH manifest within 3 days of the LP, but symptoms can occur up to 14 days later.[2] Post-dural puncture headache is commonly described as a bilateral, non-throbbing fronto-occipital headache that worsens with upright positioning and improves when supine.[3] The primary mechanism is a dural puncture that leads to persistent leakage of the CSF, which exceeds its production by the choroid plexus and causes a net decrease in CSF volume and intracranial pressure (ICP). Upright positioning then results in a downward shift of the brain, causing the stretch of pain-sensitive fibres, resulting in headache.[4] A secondary mechanism for PDPH involves compensatory activation of cerebral adenosine receptors, leading to vasodilation and increased brain volume.[5]

The probability of developing PDPH is higher in patients aged 12–19 yr (*vs* those aged less than 12 yr because of lower compliance of the epidural space), females (for unclear reasons), and patients with lower BMI (because of lack of abdominal girth and concomitant epidural pressure to shunt CSF cranially).[6–8] Most PDPHs resolve spontaneously within 7–14 days as the dura seals and the CSF volume self-equilibrates, but can persist for 6–12 months in rare cases.[9] Unresolved PDPH is associated with significant morbidity, with 39% of patients experiencing at least 1 week of impaired

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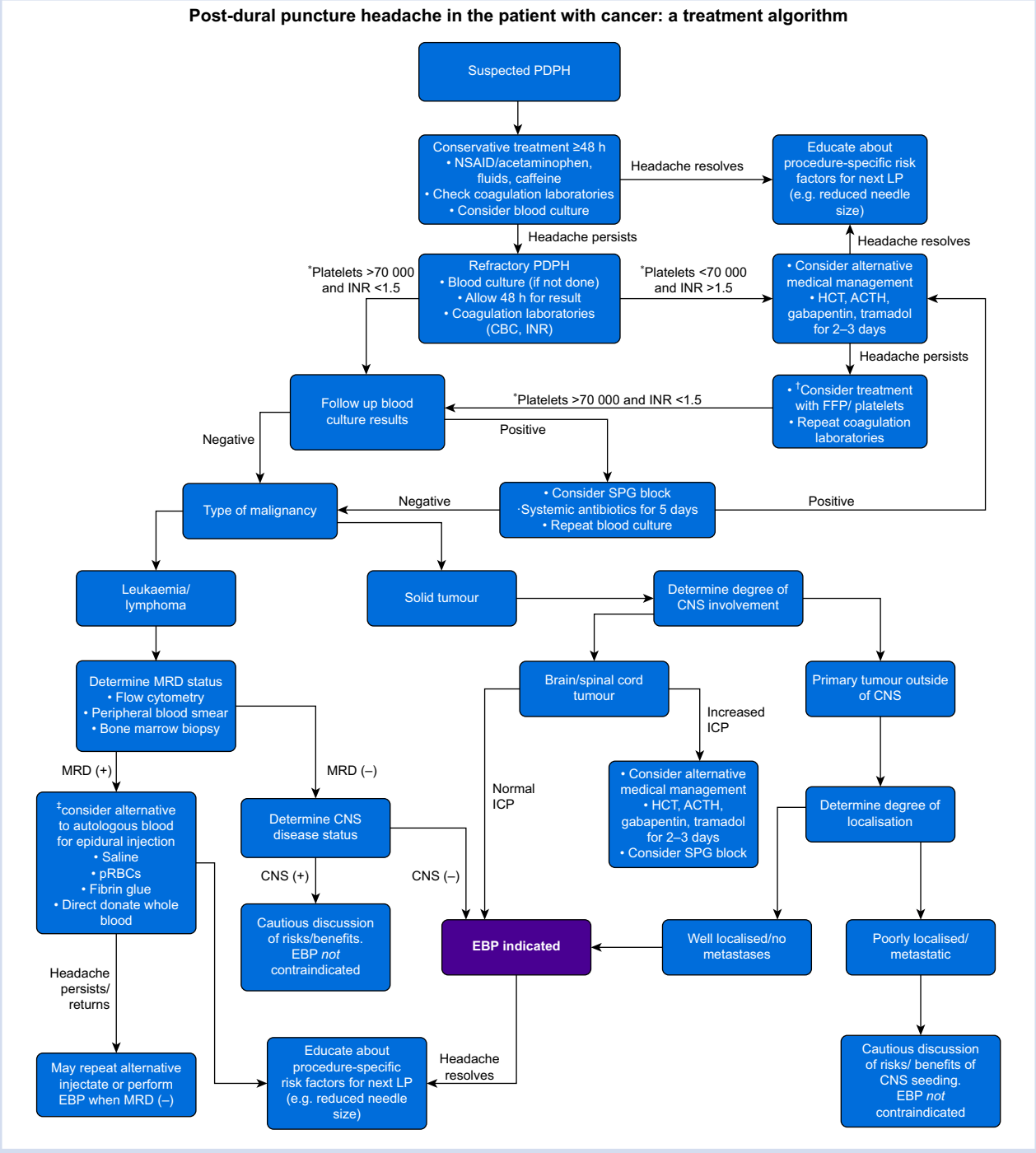

Fig 1. Clinical treatment algorithm for oncology patients with post-dural puncture headache. *Platelet count recommendation was based on conventional practice of obstetric anaesthetists. The INR recommendation was based on conventional practice for neuraxial intervention. There was no consensus guideline on the minimum platelet count or the maximum INR for safe and effective EBP. See main text for references. †Correction of hypocoagulability was based on local practices and incorporated patient-specific considerations. Factor concentrates may be considered, although they have not been previously reported in the literature. ‡Epidural injectates alternative to autologous blood have only been reported in case reports and are considered experimental in nature. Alternative medical management (see 'consider alternative medical management' box) or SPG block at this place in the algorithm may also be considered. ACTH, adrenocorticotropic hormone; ALL, acute lymphoblastic leukaemia; AML, acute myelogenous leukaemia; CBC, complete blood count; EPB, epidural blood patch; FFP, fresh frozen plasma; HCT, hydrocortisone; INR, international normalised ratio; LP, lumbar puncture; MRD, minimal residual disease; PDPH, post-dural puncture headache; pRBCs, packed red blood cells; SPG, sphenopalatine ganglion.

Table 1 Published reports of epidural space-based management of post-dural puncture headache in the oncology population (or documented consideration thereof). ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; PDPH, post-dural puncture headache.

Type of publication and author (yr)	Patient(s)	Outcome
Case report Scher and colleagues[33] (1992)	19-yr-old female with embryonal cell rhabdomyosarcoma	Autologous blood injected (15 ml); immediate relief
Case report Bucklin and colleagues[34] (1999)	27-yr-old *post-partum* female with AML	Discussed, but decided against autologous blood because of risk of neoplastic cell seeding; PDPH resolved with conservative treatment (after 10 days)
Case report Decramer and colleagues[35] (2005)	50-yr-old female with breast cancer	Fibrin glue injected (5 ml); immediate and persistent relief
Retrospective study Kokki and colleagues[30] (2012)	42 paediatric patients (2 oncology)	Autologous blood injected (mean volume: 0.27 ml kg^{-1}); complete and persistent relief in 85.4% of patients; partial or temporary relief in remaining patients
Case report Vassal and colleagues[36] (2013)	28-yr-old female with ALL	Hydroxyethyl starch injected (15 ml) with 3 h infusion at 5 ml h^{-1}; immediate and prolonged relief (15 days follow-up)
Case report Mergan and colleagues[32] (2014)	46-yr-old male with T-cell ALL	Autologous blood injected (20 ml) after negative flow cytometry and negative blood, sputum, and CSF cultures; immediate relief No new CNS disease at 3 months follow-up
Retrospective study Demaree and colleagues[1] (2017)	80 patients; mixed adult/paediatric oncology population (62 lymphoma; 18 leukaemia)	PDPH improvement in 96.2% of patients (no improvement or worsening in PDPH in 3.8%) No new CNS disease at a median follow-up of 3.74 yr

performance in activities of daily living and some requiring hospitalisation.[10]

Prevention is considered the optimal way to manage PDPH. Reducing LP needle size, utilisation of a pencil-point needle, using a steeper angle of insertion, orienting the bevel parallel with the longitudinal neuraxis (if using a cutting needle), and reinserting the stylet before needle withdrawal can reduce PDPH incidence.[11] Epidural saline injection at the time of LP has been demonstrated to reduce the rate and severity of PDPH in 33 young adult patients with acute lymphoblastic leukaemia (ALL).[12] Lastly, procedural experience plays a significant role in the incidence of PDPH, as inexperienced providers may cause multiple unrecognised dural punctures.[10] Providers with extensive experience in performing LP should perform or supervise the procedure, particularly for a patient with numerous other patient-specific risk factors. Despite these preventive strategies, PDPH still occurs, especially in oncology patients requiring repeated LPs.

This review focuses on PDPH in the oncology population, which constitutes the majority of patients receiving repeated LPs, most commonly for leukaemias and non-Hodgkin lymphomas (NHLs).[13] Patients with leukaemia or NHL undergo frequent LPs for monitoring CNS involvement and to deliver intrathecal (IT) chemotherapy, which is problematic, as the risk of PDPH increases with the cumulative number of LPs.[12] Paediatric oncology patients specifically, undergoing diagnostic or therapeutic LP, have PDPH rates of 6–9%.[5]

Although 85% of PDPH in adult patients resolves within 6 weeks with conservative management, this approach is less effective in decreasing the PDPH duration in paediatric patients.[5,11] Conservative management of PDPH involves supine positioning, increased fluid intake, caffeine administration, and oral analgesics (such as NSAIDs and acetaminophen). When conservative treatment fails or PDPH is debilitating, more-aggressive management with an epidural blood patch (EBP) may be offered.

There are no consensus recommendations for addressing this situation in the oncology population, particularly in children. To address this gap in the literature, this review summarises existing literature on the role of EBP in oncology patients, and proposes an algorithm for the treatment of PDPH in adult and paediatric patients with cancer (Fig. 1).

Epidural blood patch procedure

An EBP involves the injection of autologous blood, drawn from a peripheral vein, into the epidural space. This is commonly performed under local anaesthesia in the adult population, and under sedation or general anaesthesia in the paediatric population.[14–16] Blood spreads over several segments within the epidural space, both cranially and caudally, but likely favours the cranial direction.[17] Thus, the epidural needle does not need to be introduced at the same level as the suspected dural puncture. The patient

then remains in a reclined position for 1–2 h. Newly injected epidural blood compresses the dural sac, resulting in increased epidural and subarachnoid pressures that restore CSF pressures intracranially, thus reducing traction on pain-sensitive fibres. After ~7 h, blood attaches to the dura as a thin membrane and prevents the CSF from leaking through the build-up of organised blood.[18]

Although historically considered an aggressive management for PDPH, the use of EBP is increasing, particularly in adolescents, because conservative management is less successful in younger patients.[1,5] A 2015 Cochrane review of 24 trials (total of 2996 participants) found no evidence to support that routine bed rest after dural puncture prevents PDPH.[19] A more recent review of 13 RCTs (479 participants) demonstrated that 'high-dose' caffeine (at least 300 mg) cures PDPH in 70% of young adult patients, and compared with placebo, high-dose caffeine decreases PDPH persistence and need for supplementary interventions.[20] This dose, however, far exceeds the ~85 mg of caffeine in carbonated beverages, the most common caffeine source prescribed. Accurate paediatric dosing for caffeine in the management of non-specific headaches has been reported to be 50–100 mg for children weighing 5–35 kg.[21] However, high-dose caffeine is not typically administered to paediatric patients because of risk of CNS toxicity and atrial fibrillation.[1,5] Therefore, a 70% cure rate with caffeine may be an overestimation in the paediatric population. Lastly, the role of increased fluid intake has remained unclear and unproved, although commonly offered. If conservative methods fail or are contraindicated because of adverse effects, an EBP should be considered.

Multiple adult studies have demonstrated the efficacy of EBP in the management of PDPH, with success rates as high as 96% and even higher with repeat EBP.[1,22–27] The utilisation of EBP in the paediatric population appears to be successful as well.[11,28–30] A 2002 retrospective study reported that EBP with 0.13–0.46 ml kg^{-1} of blood given to five children (<12 yr old) with PDPH completely relieved symptoms in four patients (and slightly relieved them in the fifth) and caused no adverse effects.[29] Another similar study on patients aged 13–18 yr given a mean of 0.2 ml kg^{-1} of autologous blood epidurally reported an efficacy of 93%.[28] Injection volume must be especially considered in paediatric patients, as they are likely to be sedated or anaesthetised during the EBP procedure and unable to provide verbal feedback on the development of elevated lumbar epidural pressure, and over-injection can lead to nerve root irritation and radicular pain.[17] Demonstrated efficacy, along with few reported complications, makes EBP the treatment of choice for refractory PDPH, especially in patients at high risk of PDPH attributable to multiple LPs, such as oncology patients.[31]

Use of EBPs in oncology patients is met with hesitation because of risk of seeding the CNS with neoplastic cells (either blood-borne or circulating solid tumour) and increased risk of CNS infection in immunocompromised patients.[32] Case reports, consisting mostly of adult patients, present various approaches to this clinical dilemma (Table 1), and a recent study has reported the safety of EBP in patients with mixed oncological diagnoses.[1] Given the paucity of paediatric-specific literature and similar pathophysiology and treatment protocols, we include adult EBP data for common paediatric malignancies.

Results

Acute myelogenous leukaemia

Acute myelogenous leukaemia (AML) accounts for 15–20% of paediatric acute leukaemias. Current therapies cure ~60–70% of children utilising weekly or monthly IT chemotherapy (depending on CNS disease at diagnosis).[31,37] A 2005 prospective 18 month study reporting the effects of 247 IT chemotherapy injections delivered via a variety of differently sized spinal needles (22-gauge to 27-gauge needles) to children with leukaemia demonstrated a PDPH rate of 8.9%.[4] The use of EBP to treat PDPH in patients with AML is limited because of concerns of CNS seeding and infection. However, a 13 yr retrospective study suggested the safe use of EBP in a mixed oncology population, which included multiple patients with leukaemia (subtype not reported).[1] All 18 patients with leukaemia had complete symptom relief with EBP. Importantly, there was no evidence of neoplastic cell seeding to the CNS at a median follow-up of 5.63 yr.[1]

Acute lymphoblastic leukaemia

ALL is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood, and extramedullary sites. Approximately 80% of ALL cases occur in children.[38] Regardless of the treatment protocol, a crucial component is CNS prophylaxis with IT chemotherapy given at specific intervals throughout therapy, with some protocols utilising 27 LPs over 2.5 yr of treatment.[8,38] The numerous LPs correlate with a high incidence of PDPH in patients with ALL. A 2005 prospective study demonstrated that amongst 47 paediatric patients (42 ALL and 5 AML), 14% developed PDPH.[4] Additionally, a 2008 patient questionnaire on PDPH after LP in paediatric patients with ALL demonstrated that 11% and 7% developed PDPH after LP with the 22G Quincke needle and 25G pencil-point needle, respectively.[39]

Despite the established relationship between repeated LP and PDPH, there are no large trials on EBP in paediatric patients with ALL. An adult case report of a 46-yr-old man with T-cell ALL who developed PDPH after multiple IT methotrexate injections demonstrated the safe and efficacious use of an EBP after a discussion with his oncologist.[32] Before the procedure, blood, sputum, and CSF were cultured to assess occult infection, and peripheral blood flow cytometry was performed to screen for circulating blasts. After negative cultures and flow cytometry, 20 ml of autologous blood was injected into the epidural space. The patient had complete pain relief and no CNS disease at the 3 months follow-up.[32] Although this case does not validate the use of EBP in paediatric patients with ALL, it gives a framework for approaching EBP in the general oncological population (Fig. 1).

Non-Hodgkin lymphoma

Patients with NHL have a high risk for CNS involvement, which is associated with poor outcomes; therefore, four to eight treatments of IT methotrexate are usually included as

part of primary therapy.[40] Despite the frequency of IT treatments, EBP is not well studied in paediatric lymphoma. In a retrospective review, 59 of 62 patients with lymphoma (median age: 45.1 yr) with PDPH had symptom relief with EBP. Importantly, as with the leukaemia population, that study found no evidence of neoplastic cells seeding the CNS.[1]

Solid tumours

Solid tumours constitute ~30% of all paediatric cancers.[41] For these patients, LPs are performed only when there is CNS involvement.

Patients with intracranial tumours have a high likelihood of persistent headaches, which may be related to increased ICP (secondary to tumour, brain swelling, and CSF obstruction), surgery, medications, or other causes.[42] An EBP has no role in treating headaches secondary to these causes. If the headache is likely related to a thoracolumbar CSF leak (related to LP or not), EBP may be considered. However, if an intracranial tumour causes a midline or downward shift (with or without CSF obstruction), EBP is contraindicated because of the high risk of herniation with unintended dural puncture.[43] If the intracranial tumour has no mass effect, hydrocephalus, or radiographic or clinical symptoms of increased ICP, neuraxial intervention (including EBP) is unlikely to cause herniation.[43] However, particular care with regard to epidural injection volume must be given in the setting of increased ICP, as higher injection volumes could further elevate ICP. Neurological deterioration after EBP in the setting of increased ICP has been reported.[44] Further, risk of CNS seeding of neoplastic cells with EBP is less concerning, given the relative ratio of malignant cells already present in the CNS *vs* peripheral blood.

Although the incidence of PDPH in patients with solid tumours appears low, EBP might be indicated, such as in the case report of a 19-yr-old patient with rhabdomyosarcoma who developed PDPH after diagnostic LP.[33] In such instances, the risks and benefits of the procedure, including degree of tumour localisation (*vs* presence of circulating malignant cells), should be discussed amongst the anaesthetist, patient, and oncologist.

Discussion

The two primary concerns for using EBP in patients with cancer are the risk of neuraxial seeding of neoplastic cells into the CNS and risk of infection, given their (likely) immunocompromised state. A third concern, although not unique to patients with cancer, is coagulopathy, which is more common in this population.

The mechanism of neoplastic seeding in patients with leukaemia or lymphoma is not completely understood, but it may involve the upregulation of molecules, such as vascular endothelial growth factor and vascular adhesion molecule by neoplastic cells. These may lead to disruption of the blood–brain barrier (BBB) and escape of neoplastic cells from the vasculature into the CNS; therefore, CSF is surveilled by repeated LPs for the presence of neoplastic cells.[1] For neuraxial seeding to occur by EBP, the patient's blood must contain circulating blasts with specific molecular factors at the time of injection, or the procedure must cause an accidental dural puncture, thus violating the BBB. However, the risk of accidental dural puncture is ever-present with the routine use of neuraxial anaesthesia, but does not typically preclude its use in the oncology population (e.g. epidural catheter placement for abdominal tumour resection).

It is paramount to minimise the risk of CNS seeding during procedures by determining the patient's minimal residual disease (MRD) status (number of leukaemic cells present) by flow cytometry. This method is highly sensitive in detecting blasts in peripheral blood or bone marrow, and is periodically performed throughout cancer treatment to evaluate response. Such methods can be used to stratify the risk of CNS seeding in patients. A patient should have a 'negative flow' (<0.1% or lower) in a recent peripheral blood sample (indicating the absence of blasts in circulating blood) before EBP. This approach was used in a case report of a 46-yr-old male with T-cell ALL, and the patient remained free of CNS disease at the 3 months follow-up and achieved complete PDPH resolution.[32] If a patient with cancer has an unknown (or not recently evaluated) MRD status, or if MRD is detectable, a discussion of procedural risks and benefits is recommended amongst the anaesthetist, oncologist, and patient/guardian. Maximising non-interventional approaches and advising prolonged bed rest are indicated.

If procedural intervention is warranted, but the risk of CNS seeding secondary to EBP is considered too high, injectable alternatives to autologous blood, such as fibrin glue, saline, colloid solutions, donated packed red blood cells (pRBCs), and irradiated pRBCs, can be considered (Fig. 1). A case report of a 50-yr-old female developing severe PDPH after lobectomy described the successful use of fibrin glue administered into the epidural space.[35] The use of fibrin glue is limited because of possible severe adverse sequelae, such as viral or aseptic meningitis, intravascular thrombosis, and anaphylaxis.[1] Although fibrin glue can seal the hole in the dura through formation of a plasma clot, it has minimal 'volume-based' benefit. Thus, patients may not have symptomatic relief until the choroid plexus generates CSF to replace that which had already leaked out of the dural sac.

Evidence for epidural saline as a reliable alternative to autologous blood is equivocal. A 2004 study demonstrated that saline did not provide the same extent of symptom relief as did autologous blood.[45] The primary disadvantage of epidural saline is that a single injection cannot provide prolonged analgesia; thus, repeated injections or a continuous epidural infusion is needed. A 15-yr-old patient developing PDPH after IT chemotherapy was successfully administered a gelatinous saline and colloid mixture, but it only provided analgesia for 3 h.[30] Subsequently, an EBP using autologous blood was performed, which fully resolved the PDPH.[30] Additional studies have reported the use of various colloid solutions (e.g. dextran and hydroxyethyl starch) to manage PDPH when autologous blood is contraindicated, with mixed results. Although colloid solutions may remain in the epidural space longer than saline does, they do not seal the dural hole and there is a high likelihood of recurrence.[46]

Blood-based alternatives to autologous blood include donated whole blood and irradiated pRBCs. Donated whole blood has been used successfully in patients with PDPH and known systemic infections or ongoing fevers.[47,48] A high level of coordination is required, as the donor must be present at the time of the EBP. Further, the donor must be screened for infectious disease and cross-matched to ensure allogenicity before the procedure. There exists, however, a risk of graft *vs* host disease in immunocompromised patients with cancer. Leucoreduction and irradiation could minimise these risks, but this combination has not been previously reported. The

high-level coordination required can make this approach unfavourable.

Irradiating blood theoretically destroys leukaemic blasts, and it is postulated that using irradiated pRBCs for EBP reduces the risk of CNS seeding. This may be feasible for patients with an indication for EBP who have detectable circulating disease and no alternatives. Although irradiating pRBCs drastically reduces the risk of graft *vs* host disease, it might still occur in immunocompromised patients, including oncology patients. Further, it is unlikely that pRBCs alone, irradiated or not, without clotting factors or platelets, would seal a dural hole. Stored pRBCs would also contain citrate, again limiting the likelihood of EBP, providing prolonged relief related to lack of thrombus formation. The use of irradiated pRBCs for this purpose has been proposed, but no studies have been reported to date.

Known bacteraemia is an absolute contraindication to EBP. However, the concern with EBP in the oncology (immunocompromised) population is related to risk of CNS infection in the setting of non-known (occult) bacteraemia. This risk is two-fold: (i) risk of introducing bacteria into the CSF, leading to meningitis; and (ii) risk of bacteria in the blood being injected into the epidural space, leading to epidural abscess. However, neuraxial interventions are routinely performed in immunocompromised patients (for diagnostic/therapeutic indications and for anaesthesia/pain management). Although more frequent than for patients with intact immune function, neuraxial infections are rare.[49] Most epidural infections that develop secondary to a neuraxial intervention are related to long-term (>3 days) catheter placement rather than singular injections.[50] In six immunocompromised human immunodeficiency virus-positive patients who had an EBP and were followed for 6–24 months, there was no increase in CNS morbidity related to EBP.[51] This study suggests that neither viraemia nor immunocompromised status is directly linked to CNS infection after EBP.

Nevertheless, infectious complications should always be mentioned as a risk of any neuraxial intervention. However, infectious risk is rarely cited as a reason for forgoing the procedure entirely (in patients *without* known bacteraemia). It is reasonable to suspect, however, that oncology patients may have a higher incidence of *occult* bacteraemia than the general PDPH population, given the increased prevalence of indwelling central venous catheters and the immunocompromised state. Therefore, it is prudent to perform peripheral blood cultures before EBP to rule out occult bacteraemia or even treat them with prophylactic antibiotics as previously reported.[32]

A third concern of EBP use in the oncology population relates to the coagulation status of the patient. Routine evaluation of the coagulation profile must be performed before any neuraxial procedure for all patients. It is not uncommon for patients with cancer to have thrombocytopenia related to bone marrow suppression, or coagulation abnormalities secondary to chemotherapy, liver dysfunction, or malnutrition. Each of these factors must be evaluated before performing EBP, and, at minimum, a platelet count and international normalised ratio (INR) should be obtained. Correction of laboratory abnormalities (with blood products or supplements) and withholding of anticoagulant medications as clinically indicated are necessary. Although there is no consensus platelet count before EPB, reasonable comparisons can be drawn to the practice observed for labour epidural placement in the obstetric population, where most anaesthetists will place an epidural catheter in a patient with a stable platelet count of 70, 000 μl^{-1}.[52] Conventionally, an INR of $\leq$1.5 is a safe threshold for epidural placement.[53]

Given the risks delineated here, it is imperative that a personalised approach be undertaken for each patient with PDPH in the setting of malignancy. The treatment team should weigh the severity of and debilitation caused by the headache, with the potential oncological, infectious, and haematological risks of the procedure. For a patient on active chemotherapy with pancytopaenia and a mild-to-moderate headache, a more conservative approach (i.e. non-interventional) is preferred. Conversely, for a patient with known malignancy but adequate blood count recovery and a debilitating headache, a more aggressive approach may be justified. Special consideration for the paediatric patient is warranted, given the need for sedation/anaesthesia to perform the EBP, which may shift the risk–benefit balance depending on the overall condition of the child. The risk of sedation/anaesthesia alone may preclude the ability to safely perform the EBP, regardless of the severity of the headache.

Conclusions

Prevention of a post-dural puncture headache via the optimisation of patient- and procedure-specific risk factors is essential. Despite these steps, post-dural puncture headaches occur and an epidural blood patch is appropriate to consider in a subset of patients with cancer. Despite limited evidence demonstrating the safety of epidural blood patch use in the oncology population, the presence of a malignancy is not an absolute contraindication to the use of epidural blood patch in the management of post-dural puncture headache. To date, no adverse events have been reported.[11,30] Utilisation of an epidural blood patch in the oncology population should be considered if conservative management fails, and after extensively evaluating patient-specific risks and benefits together with the anaesthetist, patient (or family), and oncologist.

Authors' contributions

Literature review: KJM
Writing of paper: RM, KJM
Critical review of paper: SEK, JF
Project direction: SEK, JF
All authors gave final approval for the version to be published, and they agree to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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