Management of cardiac arrest during neurosurgery in adults

Guidelines for healthcare providers

Working Group of the Resuscitation Council (UK), Neuroanaesthesia Society of Great Britain and Ireland and Society of British Neurological Surgeons.

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Executive summary

1. This guidance covers the management of cardiac arrest during neurosurgery in adult patients. It is intended for all members of the team; surgeons, anaesthetists and theatre staff.
2. Cardiac arrest during anaesthesia for adult non-cardiac surgery is relatively uncommon, with a reported incidence of 0.01–0.34%. Its incidence in neurosurgical patients is unknown.
3. When cardiac arrest does occur, it should be managed using the 'Cardiac Arrest in Neurosurgery algorithm' in conjunction with current Advanced Life Support (ALS) guidelines.
4. If the initial rhythm is asystole, it is essential to ensure all potential surgical causes are eliminated.
5. The pre-emptive use of an anticholinergic drug should be considered in patients at high risk of severe bradycardia or asystole.
6. Patients at risk of venous air embolism (VAE) should have appropriate monitoring to allow early detection and treatment. Transthoracic ultrasound may aid in the confirmation of diagnosis.
7. Patients in either the supine or prone position, who have a cardiac arrest, should have chest compressions and/or defibrillation started without any initial change of their position.
8. Patients in the lateral or sitting position should be placed in the supine position to perform CPR, along with those in the prone position in whom chest compressions are ineffective.
9. Efficacy of CPR should be judged using end-tidal CO_2 concentration, arterial pressure and waveform to support clinical assessment.
10. If the patient's head is fixed in the Mayfield® skull clamp, consider early release of the clamp from the operating table.
11. Discuss the possibility of emergency repositioning before the start of anaesthesia and surgery, with clear allocation of roles and responsibilities.
12. All members of the team should practise the process of placing a patient in a safe position to allow CPR and defibrillation.
13. Following successful resuscitation, plan further management including the need for investigations, (e.g. ultrasound or MRI/CT).
14. Accurate and contemporaneous record of the event and actions taken should be kept which must be legible, timed, dated and signed.
15. The incident should be reported via the National Reporting and Learning System (NRLS) or local patient safety incident reporting processes.
16. All staff should be offered the opportunity for personal and emotional support.

17. All cases should be reviewed at the local morbidity and mortality meeting or equivalent, to encourage openness, continuous learning and service improvement.

Scope

This guidance covers the management of cardiac arrest during neurosurgery in adult patients. It is intended for all members of the team; surgeons, anaesthetists and theatre staff. The guidance is also applicable to adult patients undergoing neuroradiological procedures or spinal surgery in the prone position. It addresses the specific actions that will be required in a neurosurgical patient to allow safe and effective cardiopulmonary resuscitation (CPR) and should be read in conjunction with the current Resuscitation Council (UK) Guidelines www.resus.org.uk/pages/guide.htm.

Methods

This guidance was produced according to the Resuscitation Council (UK) Development Process Manual (2014). The specific process for this guidance is documented in Appendix 1.

Introduction

Cardiac arrest during anaesthesia for adult non-cardiac surgery occurs with a reported incidence of 0.01–0.34%.[1-3] Such a wide variation is due to a number of factors including definition of cardiac arrest, heterogeneity of patient groups and type of surgery performed. In a report of operating room morbidity and mortality in Japanese hospitals, during 2 363 038 cases, the incidence of cardiac arrest during surgery was 7.12 per 10 000 cases. Principle cause of cardiac arrest during anaesthesia was massive haemorrhage (31.9%). Human error was implicated in 53% of cardiac arrests and 22% were totally attributable to anaesthesia.[4] In a large American survey at a tertiary referral centre, 35% of cardiac arrests were related to bleeding, 44% to cardiac causes and 21% to other causes.[5]

Cardiac arrest during anaesthesia and surgery occurs in closely observed, monitored patients. In many cases the cause of the cardiac arrest may be known or the arrest anticipated. Intravenous access will most likely be already established, with drugs and defibrillation readily accessible; not surprisingly therefore, survival approaches 50%[5] and when solely anaesthesia-related, survival approaching 80% has been reported.[6,7]

CPR in the anaesthetised neurosurgical patient

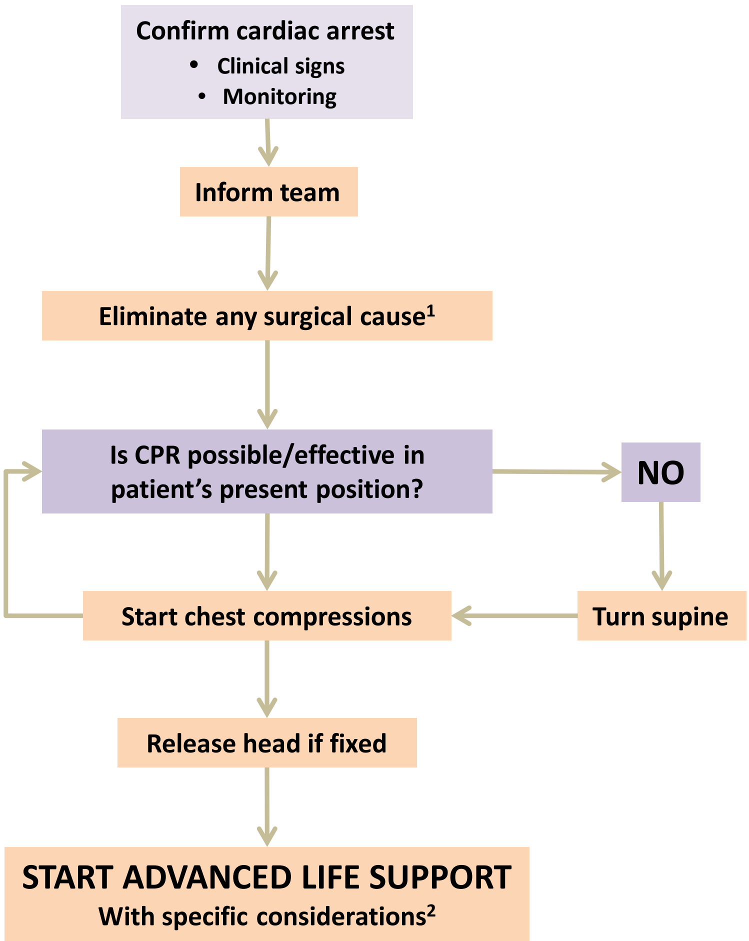
The majority of neurosurgical patients will be intubated and have end-tidal carbon dioxide ($etCO_2$) monitoring and an indwelling arterial cannula for direct blood pressure monitoring. Both monitors can be used to confirm the clinical diagnosis of cardiac arrest, provide a useful guide to the quality of CPR in terms of the efficacy of chest compressions and indicate the return of a spontaneous circulation (ROSC).[8-16]

Once cardiac arrest has been confirmed, start resuscitation and rapidly check the following.

1. The patient is being ventilated:
    - the tube is not obstructed, kinked or displaced either out of the trachea or into a main bronchus
    - the patient has not become disconnected from the ventilator
    - there is an appropriate concentration of inspired oxygen.
2. All anaesthetic drugs have or are being given at the correct dose and rate
3. There has not been a sudden unidentified loss of blood.

Management of cardiac arrest should follow the Cardiac Arrest in Neurosurgery (CAN) algorithm (Figure 1), supported by the current Advanced Life Support (ALS) guidelines.[17] The only variation from the ALS guidelines is the initial dose of adrenaline; give the first dose in increments (e.g. 50–100 micrograms), rather than a 1 mg bolus. This will help limit any rebound hypertension and reduce the risk of haemorrhage if resuscitation is successful rapidly. If 1 mg in total has been given with no response, give further adrenaline doses of 1 mg. Identification and treatment of the underlying cause, if reversible, in these circumstances is most likely to lead to successful resuscitation, bearing in mind that some reversible causes (e.g. haemorrhage, local anaesthetic toxicity) can require a prolonged resuscitation attempt.

The Cardiac Arrest in Neurosurgery algorithm



SURGICAL CONSIDERATIONS

- [1]Eliminate any surgical cause
  - Asystole: retraction, instrumentation
  - Venous air embolism: flood field with saline, put patient head down if possible
- Attend to wound:
  - Control haemorrhage
  - Protect against trauma
  - Minimise contamination
- Stop surgery as soon as possible

[2]SPECIFIC CONSIDERATIONS FOR ALS

- Ensure correct tracheal tube position and ventilation
- Ventilate with 100% oxygen
- Get senior help
- Follow major haemorrhage protocol
- Give initial adrenaline doses as 50-100µg boluses IV
- Echocardiography to check for VAE

Figure 1. The Cardiac Arrest in Neurosurgery algorithm

Specific factors influencing CPR in neurosurgical patients

These can be divided into three main groups:

1. The surgical procedure.
2. The position of the patient.
3. Performing CPR on a patient with an open wound.

1. The surgical procedure

Operations on the anterior hypothalamus, brain stem, cerebello-pontine angle, pituitary, and trigeminal nerve, neuro-endoscopy and the use of irrigation fluid of the wrong temperature, are all associated with arrhythmias, usually severe bradycardia with associated hypotension or asystole.

Severe bradycardia and asystole

A common cause is activation of the trigemino-cardiac reflex. Mostly this will respond to the removal of the cause (e.g. surgical instrumentation or traction). If the bradycardia persists, give atropine 500–600 micrograms IV (up to a maximum of 3 mg). Glycopyrronium bromide (glycopyrrolate) is an alternative and has the theoretical advantage of not crossing the blood brain barrier. The dose is 4–5 micrograms kg^{-1} up to a maximum of 400 micrograms, which may be repeated once. If no response is obtained following removal of any surgical stimulation and the use of an anticholinergic, use an adrenaline infusion 2–10 micrograms min^{-1} in accordance with the RC (UK) bradycardia algorithm http://www.resus.org.uk/pages/bradpost.pdf

Early use of transcutaneous pacing has been suggested for use in patients with a bradycardia who are unresponsive to adrenaline.[18,19]

In patients at high risk of bradycardia, consider pre-emptive use of an anticholinergic drug. Although this may prevent a bradycardia, it will also result in the loss of the indication of surgical encroachment on vital areas and the surgeon should be warned.

If the patient becomes asystolic, follow the CAN algorithm; ensure that all potential surgical causes are removed. If there is no return of circulation, commence CPR as soon as possible (see below) and give further treatment based on the ALS guidelines.

Venous air embolism

Venous air embolism (VAE) is the result of entrainment of air into the venous circulation. It is more common if the venous sinuses are opened with the head elevated above the level of the heart, and is maximal in the sitting position,[20,21] but has also been reported during supine infratentorial intracranial surgery[22] and spinal surgery.[23,24] Oxygen embolism has also been reported during the use of hydrogen peroxide as a haemostatic agent.[25] The volume of entrained air to cause significant injury in adults is unknown but has been estimated to be 3–5 ml kg^{-1}, [26] with the greater the rate of entrainment, the smaller the lethal volume.[27]

Signs of venous air embolism[27]

In most cases where VAE is unexpected, the initial presentation may be indicated by:

- $etCO_2$ – a fall of 2 mmHg (0.25 kPa) may indicate VAE, but is not specific. The concentration may also be reduced by concomitant hypotension
- ECG – ST segment and T wave changes initially, followed by supraventricular and ventricular tachyarrythmias
- hypotension, progressing to PEA.

In high-risk cases, specific methods may be used to identify VAE early before cardiac arrest occurs. The most sensitive is transoesophageal echocardiography (TOE) which can detect a bolus of air of 0.02 mL/kg. However use of TOE is not always practical due to extreme neck flexion, and poor access to reposition the probe. Others methods include a pulmonary artery catheter (VAE causes a rise in the pulmonary artery pressure) and monitoring end-tidal nitrogen (increases in VAE), but in UK practice these are not commonly used. A precordial Doppler probe, although not as sensitive as TOE, is still commonly used and remains an effective means of detecting larger emboli. Auscultation using either a precordial or oesophageal stethoscope to identify a 'mill-wheel' murmur is no longer used.

Treatment of VAE

If VAE is suspected and **the patient still has a pulse**, the immediate response should be to try to prevent further entrainment of air by:

- flooding the surgical field with saline or lactated Ringer's solution
- manoeuvres to raise venous pressure to a level greater than atmospheric pressure:
  - position the patient supine or head down
  - manually compress the jugular veins[28]
  - increase intrathoracic pressure using positive end expiratory pressure (PEEP). This is controversial; it may decrease the incidence of VAE and allow

identification of site of air entry[29,30] but increases the risk of paradoxical air embolism in those with a potential for this (e.g. a patent foramen ovale).[31, 32] In addition the adverse haemodynamic effects of PEEP, especially in the sitting position must be considered.

Specific treatment:

- stop nitrous oxide if being used, give 100% oxygen
- haemodynamic support; VAE increases right ventricular afterload, resulting in acute right ventricular failure and a subsequent decrease in left ventricular output
  - volume expansion; IV fluids
  - inotropes; an infusion of either dobutamine (5–20 microgram kg^{-1} min^{-1}) or, adrenaline (0.05–1.0 microgram kg^{-1} min^{-1}).
- attempt aspiration via central venous catheter if one is already in situ. There is no evidence to support the emergency insertion of a standard catheter, however a specific catheter has been designed (Bunegin-Albin Air Aspiration Set, Cook Medical) which has been shown to be effective in a dog model of VAE[33]
- if the patient has a cardiac arrest, follow the CAN algorithm (Figure 1)
- if transthoracic ultrasound is available, this can be used to confirm the diagnosis and guide treatment.

There is some evidence from research in animals that chest compressions are beneficial for treatment of severe hypotension after VAE before cardiac arrest occurs. The rationale is that chest compressions force air out of the right ventricular outflow tract into the smaller pulmonary vessels, thus improving forward blood flow.

There is no evidence in humans or animals to support putting the patient in the left lateral position to shift air to the non-dependent parts of the right ventricle and reduce outflow obstruction.

2. The position of the patient

Neurosurgery is carried out with the patient in one of four positions; supine, lateral, prone and sitting. In addition, for many intracranial and upper cervical spine procedures, the patient's head is held in a rigid, fixed position using a clamp; one end is fixed to the patient via three pins embedded into the skull and the other end is fixed to the operating table (Mayfield® skull clamp). This prevents any movement of the head, a requirement during certain neurosurgical procedures (e.g. the use of an operating microscope, frameless stereotaxic surgery). Management of a patient with their head fixed in a clamp is described in detail for a patient in the supine position. The same principles apply to patients in any of the other positions.

Supine position

Access to the patient in order to perform chest compressions and attach defibrillator pads should be relatively straight forward. However, any attempt to perform chest compressions with the head in the Mayfield® skull clamp ('in pins') risks causing injury to the scalp, skull and cervical spine as the torso is moved against a fixed head. A similar effect may also occur as a result of involuntary movement if defibrillation is carried out. It has been proposed that the head should be removed from the pins before defibrillation in order to reduce the risk of injury.[34] It would be reasonable to adopt the same approach before chest compressions. A faster and safer process may be to release the clamp from the operating table rather than trying to release the head from the pins. This reduces the risk of injuring the scalp, leaving a bleeding pin-hole or the operator being injured by the pins. In addition it provides a secure means of holding the patient's head during any move. There is also a theoretical risk of defibrillation causing burns at the site of insertion of the pins. In two case reports of patients who were defibrillated whilst remaining in pins, no mention is made of any apparent injury due to burns at the site of entry into the scalp and skull.[35,36] Commence CPR whilst the surgeon supports the patient's head. If defibrillation is required, then either the support for the head ('horse-shoe' type) must be attached to the operating table or the patient moved bodily along the table to provide a secure rest for the patient's head. Ensure that the surgeon (or any other person) is not in contact with the patient when the shock is delivered.

Lateral position

Although performing chest compressions on a patient in the lateral position has been described,[37] its efficacy is unknown. Therefore the patient should be turned supine as quickly and safely as possible. If defibrillation is indicated in the left or right lateral position, application of the pad over the cardiac apex or below the right clavicle respectively, is likely to be impeded. Therefore use of the anteroposterior position is recommended; one pad over the left precordium and the other just inferior to the left scapula.

Prone position

There is no immediate need to turn the patient to the supine position; CPR should be started with the patient in the prone position. In studies on small groups of patients in intensive care, who were recently deceased or had failed conventional chest compression, posterior compression generated higher mean arterial pressures than anterior compression.[38,39]

Successful resuscitation following posterior compression, using either a one or two-handed technique, with or without counter pressure on the sternum, has been reported.[40-45] At the same time as CPR is started, remove any surgical instruments from the wound and pack the wound to reduce blood loss. If the patient's head is fixed in pins, they should be managed as described above. Some patients will be positioned prone with the aid of a frame (e.g. Wilson frame, Relton-Hall frame) or pillows to allow free movement of the chest and abdomen and prevent obstruction of venous return during surgery. Effective chest compression may not be possible or effective in these circumstances unless counter pressure from a solid surface is applied.[46] If the patient is on blocks, it may be possible to reposition the one under the chest to provide a suitable solid surface. The presence of an arterial cannula and $etCO_2$ monitoring can be used to guide the effectiveness of chest compressions. Successful defibrillation in the prone position has also been described[35] and if required, pads can be applied either postero-lateral (one in the left mid-axillary line, the other over the right scapula) or bi-axillary positions.

If chest compressions are ineffective, as judged by arterial blood pressure monitoring, $etCO_2$ concentration or lack of a central pulse, the anaesthetic and surgical team must turn the patient supine as described below. Achieving this may be difficult, time-consuming and dangerous due to the presence of an open wound or an unstable spine. Once supine, surgical access becomes difficult if not impossible, which may lead to problems with haemorrhage control.[47]

Sitting position

This position is achieved by placing the patient in a special chair or operating table that can be converted to achieve a sitting position and the patient's head is usually fixed using a clamp. Although there is usually access to the thorax to allow defibrillation, chest compressions will not be possible and so the patient should be placed in the supine position. The head will need to be removed from any fixed support, or if a clamp has been used, it should be removed or released from the operating table.

3. Performing CPR on a patient with an open wound

Any patient with an open wound, who requires CPR, with or without the need to be turned into the supine position, should have any instruments removed to prevent accidental tissue injury. Protect the wound with a saline-soaked swab and then cover it with an adhesive dressing. Once this has been achieved, the process of turning the patient supine, if required, is conducted as described below. There are no reports of cerebral injury caused by CPR in patients with an open cranium. However, following successful resuscitation, control of bleeding from the surgical site, particularly a posterior one, may be problematic.[47]

Emergency repositioning of a patient

All neurosurgical teams (surgeons, anaesthetists and theatre staff) should practise the process of placing a patient in a safe position to allow CPR and defibrillation. If there is a potential need for urgent repositioning of the patient during the surgical procedure, discuss this before anaesthesia and surgery, and allocate clearly roles and responsibilities. Check the location of:

- the nearest resuscitation trolley/defibrillator
- a trolley or bed on to which the patient can be turned
- the horse-shoe head rest
- additional staff to assist with repositioning.

Suggested actions

If chest compressions are ineffective (as described above) and/or defibrillation cannot be achieved safely, the patient must be turned supine. The anaesthetist should inform all staff present in theatre and ask them to adopt their allocated roles. If CPR is required and the patient is positioned prone with a firm chest support (e.g. Montreal mattress), start chest compressions while the following actions are taken to allow the patient to be turned to a supine position.

Specific roles:

- scrub practitioner – soak a large swab in saline and obtain an adhesive dressing
- lead surgeon – remove instruments, apply pack and dressing, and support the patient's head
- surgical assistant – if the head is held by the Mayfield® clamp, disconnect, unlock and rotate it out of the way to gain more access to allow the patient's head to be turned in line with their trunk
- anaesthetist – ensure ventilator tubing is free to allow the patient to be turned without accidental extubation. Ensure all vascular lines, monitoring, catheters, etc. are free to allow disconnection if required, before turning
- anaesthetic assistant – release any devices used to secure limbs.

The theatre floor staff should:

- collect the horse-shoe head rest and make it available to surgical team

- obtain a trolley or bed
- get additional staff to help with turning of the patient
- collect a defibrillator if one is not already in the operating theatre.

Turning the patient on to a bed or trolley

1. The lead surgeon takes responsibility for the patient's head and coordinates the turn.
2. The trolley/bed is placed alongside the operating table, and the brake applied.
3. Three members of staff stand on the far side of the patient.
4. Three members of staff stand along the side of the trolley/bed with their arms placed on the top of the trolley/bed.
5. If possible the operating table is tilted laterally to assist with the turn.
6. The anaesthetist disconnects the ventilator tubing from the tracheal tube and any intravascular lines as necessary.
7. The anaesthetist informs the surgeon that the patient is ready to be turned.
8. The surgeon then gives the command for the staff against the side of the operating table to roll the patient on to the outstretched arms of the staff against the trolley/bed.
9. Once supine, chest compressions must be resumed without delay.
10. The anaesthetist reconnects the ventilator tubing and vascular lines.
11. The ECG, arterial pressure and $etCO_2$ monitors are checked.
12. Use $etCO_2$ and/or arterial waveform to ensure quality of chest compressions and detect signs of ROSC.

Points to consider:

- In patients at high risk of an arrhythmia who are not supine or where access is restricted, apply adhesive defibrillation pads before the patient is positioned and surgery commences. They can be used for monitoring, defibrillation, cardioversion and pacing.
- In adult patients with an indwelling arterial catheter displaying the blood pressure, give adrenaline in 50 microgram IV increments during cardiovascular collapse and onset of PEA/asystole. If there is no ROSC within the first few minutes of CPR, and 1 mg in total of adrenaline has been given, give further doses of adrenaline of 1 mg.
- Early use of echocardiography to guide diagnosis and treatment, especially if patient in PEA.[48]

Post-resuscitation management

Immediate surgical management

- The surgical and nursing team should 're-scrub'.
- Re-drape the patient or apply additional draping to minimise any further wound contamination.
- Irrigate the wound with copious volumes of warm (body temperature) normal saline or lactated Ringer's solution.
- Haemostasis should be secured.
- Consider further surgical options:
  - continue with the planned procedure
  - change the goals of surgical procedure
  - abandon surgery and expedited wound closure.
- Consider peri-operative imaging (ultrasound or MRI/CT) to assess for intraparenchymal haemorrhage, over drainage of CSF causing cortical collapse or a subdural haematoma.
- Consider antibiotic therapy to minimise the risk of infection due to wound contamination.
- There should be close liaison with the intensive care team regarding specific post-resuscitation care required.

Records

- An accurate and contemporaneous record of the event and actions taken should be kept. This must be legible, timed, dated and signed.
- If possible, during the event, a member of the team should be allocated to record all interventions and timings.
- If a record is made after the event, based on recollection, this should be as accurate as possible and other staff present should be asked to confirm the details.
- Where partial electronic records are used, these should be printed out, signed, dated and timed, and filed in the patient's paper health records. Where records are entirely electronic, care should be taken to ensure that the entries are detailed and accurate. A printed copy of the electronic record should also be signed, dated and timed and stored securely.
- Charts and records must not be altered in any way at a later time or date.
- All amendments must be recorded separately, timed, dated and signed.

- The incident should be reported via the National Reporting and Learning System (NRLS) www.nrls.npsa.nhs.uk/report-a-patient-safety-incident/ or by using the local patient safety incident reporting processes.

Staff management

The psychological impact on all staff of dealing with a death or major complication during surgery should not be underestimated. All hospitals must have a procedure in place to deal with and investigate such events. This must include providing personal and emotional support to those who require it. The Association of Anaesthetists of Great Britain and Ireland has produced a document outlining best practice.[49]

Learning from events

At an appropriate time, review the case at a local morbidity and mortality meeting or equivalent. In line with current practice there should be openness, trust, continuous learning and service improvement.[50] The Safe Anaesthesia Liaison Group has produced a useful toolkit for morbidity and mortality meetings www.aagbi.org/sites/default/files/SALG-M%26M-TOOLKIT-2013_0(1).pdf

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Conflicts of interest

The members confirm that they have no conflicts of interest, financial or otherwise.

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Appendix 1

Methodology

This guideline was produced according to the Resuscitation Council (UK) Development Process Manual (2014).

1. The subject of this guidance was chosen by the Executive Committee of the RC (UK) as:
    a. the Council had received several queries concerning management of cardiac arrest during neurosurgery
    b. there was no existing guidance on this topic
    c. discussions with the Neuroanaesthesia Society of Great Britain and Ireland, and Society of British Neurological Surgeons showed that there was interest in producing guidance on this topic.
2. The Executive Committee of the RC (UK) established the Working Group in July 2013.
3. The scope was established by the Working Group.
4. Literature Searches were carried out by CG and JS to identify relevant publications. There are no specific studies in this area, and the available information consisted of case reports and expert opinion. The available evidence was therefore of low or very low quality, with a high risk of bias.
5. Working group members and stakeholders identified other key documents.
6. The evidence was discussed and evaluated by the Working Group using email and a process of informal consensus. The Chair ensured that each individual on the working group was able to present and debate their views, and that discussions were open and constructive until consensus was achieved.
7. The final recommendations were formulated using the limited available evidence, the benefits and harms of treatment options, as well as the values and preferences of the Working Group and stakeholders.
8. A draft version of this guideline was made available for comment between 13 March 2014 and 28 April 2014. The following stakeholders were consulted:
    a. Resuscitation Council (UK) Executive Committee
    b. Neuroanaesthesia Society of Great Britain and Ireland
    c. Society of British Neurological Surgeons
    d. College of Operating Department Practitioners
    e. British Association of Neuroscience Nurses
    f. a resuscitation officer who has experience as a patient in a neurosurgical unit
    g. a neuroradiologist.
9. In addition the draft guidance was posted on the Resuscitation Council (UK) website www.resus.org.uk for open comment at the same time.

10. Responses (177 comments in total) were reviewed by the Working Group, and each comment addressed and when appropriate changes made.
11. The final published version as approved by the Resuscitation Council (UK), Neuroanaesthesia Society of Great Britain and Ireland, and Society of British Neurological Surgeons.
12. The guidance will be reviewed in July 2019, or earlier if necessary.

Search Strategy

PubMed, Embase and CINAHL databases were searched using the terms *cardiac arrest, heart arrest, defibrillation, craniotomy, neurosurgery, prone, prone position (*1 June 2013). This gave a total of 479 articles. The abstracts were used to identify relevant articles. The reference lists of all relevant articles were used to capture any other articles not identified in the primary search. A total of 15 articles relating to adult patients were identified. These consisted of 11 case reports, one with a systematic review of CPR in the prone position, and 4 studies in small groups of patients. There were no randomised controlled trials.

An updated search dated 9 July 2014 (Embase and Medline) identified 230 articles. This did not identify any new articles that would impact the guideline. Search terms: *((cardiac arrest or heart arrest or defibrillation) and (craniotomy or neurosurgery or prone or prone position)).mp. (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).*

Inclusion/exclusion criteria

Inclusion criteria were systematic reviews with or without meta-analyses, randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before-after (CBA) designs, interrupted time series (ITS) studies, and case-series discussion papers, non-research letters and editorials and case studies. Animal studies were excluded.

Identified articles

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