GUIDELINE FOR THE MANAGEMENT OF LONE ACUTE SEVERE HEADACHE

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For The College of Emergency Medicine
1. EXECUTIVE SUMMARY

- The Guidelines in Emergency Medicine Network (GEMNet) has been created to promote best medical practice in a range of conditions presenting to Emergency Departments in the UK.
- Each of these documents has been designed to present the best available evidence for the diagnosis and management of patients presenting to the Emergency Department.
- The document has been developed following discussion amongst Emergency Physicians to decide which topics would benefit from the development of clinical guidelines.
- The document is intended as a guideline for use in the Emergency Department by Emergency Physicians and is based on the review of the best existing evidence for the diagnostic tools and treatments available in this setting.
- The document is summarised as a Clinical Decision Support Guide that has been presented as an easy to follow algorithm.
- The intention is for each guideline to be updated and reviewed as further evidence becomes available. The formal revision date has been set at 5 years from publication though the guideline is subject to continuous informal review.

2. INTRODUCTION

2.1 Responsibility for development

This document has been developed in response to a perceived need to improve clinical effectiveness for care in this field. The Emergency Department at the Manchester Royal Infirmary has been undertaking primary and secondary research for a number of years to achieve this aim. The intention is to distil this information into practical advice for clinicians working in the department. The information is presented in the form of Clinical Decision Support Guidelines, available on shop floor in the form of a Clinical Decision Support Manual and on individual A4 sized forms.

Departmental Consultants have considered clinical conditions that may benefit from evidence based guidelines and following discussion with other clinical staff have compiled a list of topics that included Lone Severe Acute Headache.

2.2 Funding

Funding for the development for this guideline has been received from the College of Emergency Medicine.

2.3 The Guideline Working Group

A Guideline Working Group met to discuss this condition and decide on the clinical questions, consider the evidence available and develop the recommendations. The group process ensured that the working group had access to the relevant information and the required resources in order to develop in a constructive manner.

The guideline has been developed in accordance with the principles described by the National Institute for Health and Clinical Excellence guideline development methods.1
2.4 Methodology

This guideline was developed using a novel methodology that has recently been utilised in cardiothoracic surgery. Many guidelines perform a single systematic review of the literature in order to answer all of the relevant clinical questions. In order to maximize sensitivity, a separate systematic review of the literature was performed for each clinical question identified.

Guideline development was structured into several stages. Initially the lead guideline developers met to discuss the scope of the guideline and to identify all clinical questions that may have been relevant. In order to answer the clinical questions identified we performed a series of structured short-cut systematic reviews (Best Evidence Topic Summaries, BETs), the principles of which have been previously described. Where relevant BETs had already been created, the search strategies were checked and updated when necessary. The completed BETs form an appendix of this document.

Having gathered and collated the evidence for each clinical question, the principle guideline developers met to create a series of guideline recommendations, which were used to create an evidence-based flowchart following consultation with the lead guideline developer.

2.5 Levels of Evidence and Recommendation

Studies included in this guideline were graded for level of evidence according to previously accepted definitions. In summary, level 1 evidence comes from well-designed randomised controlled trials (RCT’s), level 2 evidence from large cohort studies or poorly designed RCT’s, level 3 evidence from small cohort studies or case-control studies and level 4 evidence from experimental studies, case series or case studies. The suffix ‘a’ implies that evidence at this level is from original research, whereas the suffix ‘b’ implies that the evidence is from systematic review or metaanalysis.

The recommendations that have been made were graded according to the level of evidence upon which they were based:

Grade A: Based upon multiple level 1a or 1b papers.
Grade B: Based upon individual level 1a or 1b papers or multiple level 2a or 2b papers.
Grade C: Based upon individual level 2a or 2b papers or multiple level 3a or 3b papers.
Grade D: Based upon individual level 3a or 3b papers or level 4 papers.
Grade E: Recommendations were not provided as this guideline did not seek to establish exert opinion in the absence of available evidence.
Lone Acute Severe Headache is the main presenting complaint for 1 – 2% of patients who attend the Emergency Department. Between 1-10% of such headaches may be caused by significant pathology requiring urgent investigation and management. The condition of subarachnoid haemorrhage (SAH) is an uncommon but potentially devastating cause of this symptom and so creates a diagnostic quandary.

It is necessary to select the appropriate patients to subject to further investigation without missing the significant underlying causes. Once the diagnosis has been made, appropriate treatment and necessary referrals are required.

This guideline has been designed to aid the management of adult patients presenting to Emergency Departments with the presenting complaint of a Lone, Acute, and Severe Headache. The guideline encompasses the selection of patients to apply it to, the appropriate investigations for these and then the acute treatment and disposition of these patients.

It is not intended for the guideline to be applied to patients who present with a decreased level of consciousness or have a headache in association with a clinical picture of acute sepsis. It is not intended to provide guidance for the management of patients with recurrent benign headache.

For the purposes of this guideline a lone, acute, severe headache is defined as one that comes on either instantaneously or within two minutes.

6.1 Acute headaches require investigation

Sudden or abrupt onset of a severe headache warrants further investigation to exclude serious underlying pathology.
Grade C recommendation based on level 2a studies.

6.2 Normal CT does not rule out SAH

In patients with suspected SAH and a negative CT scan lumbar puncture is necessary to exclude the diagnosis.
Grade B recommendation based on level 2a and 2b studies.

6.3 CT angiography to diagnose SAH

There is insufficient evidence to advocate the use of CT angiography for investigation of suspected SAH
There is level 3a evidence available.
6.4 Timing of lumbar puncture

Lumbar puncture is not adequate to rule out a SAH until 12h following the onset of headache.
Grade C recommendation based on a level 3b study.

6.5 Bed rest following lumbar puncture

Bed rest is not necessary following lumbar puncture.
Grade A recommendation based on level 1b evidence.

6.6 Replacement of stylet prior to needle removal after LP

Replacing the stylet before removal of the needle following LP may reduce the incidence of post-LP headaches.
Grade C recommendation based on level 2a study.

6.7 Nimodipine as treatment for SAH

Nimodipine is recommended as treatment for SAH.
Grade A recommendation based on a level 1b study.

6.8 Statins for vasospasm in SAH

There is insufficient evidence to advocate commencing a statin drug in a patient with SAH in the Emergency Department.
There is level 2a evidence available.

6.9 Mannitol as treatment for SAH

There is insufficient evidence to advocate the administration of mannitol in patients with subarachnoid haemorrhage.
No evidence was found.

6.10 Anti-fibrinolytics for the treatment of SAH

Anti-fibrinolytics are not indicated in the emergency management of subarachnoid haemorrhage.
Grade A recommendation based on level 1b studies.
Evidence used to establish the recommendations for this guideline are summarised below.

### 7.1 Acute Onset of Headaches Require Investigation

**Three part question**

In [patients presenting to an Emergency Department with headache] does [acute onset] predict [significant underlying pathology]?

**Clinical scenario**

A 57y/o man presents with a sudden onset, severe occipital headache. He has never had a headache this severe and has vomited several times. Neurological examination is normal. You request a CT scan of the patient’s brain but wonder if the acute onset of the headache is a sensitive predictor of significant underlying pathology.

The search scenario is detailed in the corresponding BET in the appendix of this paper.

**Search outcome**

2280 studies were found. Three of these papers were identified as relevant to this question.

Linn et al followed up 148 patients who had presented to their GP with a primary complaint of sudden (< 1 minute) onset of severe headache. 37 out of the 148 patients were subsequently shown to have had a subarachnoid haemorrhage. The remaining patients were followed up for a median of five years with no further incidence of SAH. Aygun et al followed 70 patients with headaches having at least one of the following features: worsening, sudden onset, persistence despite analgesia, alteration of character or associated focal neurology who underwent CT scan. Of the 31 patients with acute onset of headache, 11 had SAH and 6 had other significant pathology. None of the remaining 39 patients were subsequently shown to have SAH.

Locker et al prospectively studied 589 patients presenting to an Emergency Department with a primary complaint of non-traumatic headache over a 14 month period. Univariate analysis of the clinical features was performed followed by multivariate analysis of the features shown to be predictive of significant pathology. Sudden onset had a sensitivity of 65.6% and specificity of 62.4% as a predictor of significant pathology.

**Comments**

Only one of the studies looks at an unselected group of patients presenting to an Emergency Department with headache and attempts to qualify the important clinical features. The abrupt onset of the headache is clearly relevant in this paper alongside the other features (age over fifty and neurological abnormality). The other papers look at cohorts of patients in whom the abrupt onset of the headache is one of the inclusion criteria but this symptom remains clearly linked with significant underlying pathology, particularly subarachnoid haemorrhage.
**Recommendation**

Sudden or abrupt onset of a severe headache warrants further investigation to exclude serious underlying pathology.

Grade C recommendation based on level 2a studies.
8. GUIDELINE RECOMMENDATIONS – DIAGNOSTIC TESTS

8.1 Does a normal CT scan rule out a subarachnoid haemorrhage?

Three part question

[In patients presenting with a history of sudden severe headache] is [CT scanning alone as good as CT scanning plus lumbar puncture] in ruling out [subarachnoid hemorrhage]?

Clinical scenario

A 24 year old man who has been previously well presents to the Emergency Department complaining of headache. He describes the headache as the worst he has ever had. It came on suddenly approximately 2 hours previously and has not resolved with paracetamol. It was so severe as to cause him to collapse when it started. He has no other neurological symptoms and clinical examination reveals no neurological signs. You are concerned that he may have had a subarachnoid hemorrhage and arrange a CT scan. The CT is reported as normal. You wonder if this rules out the diagnosis of subarachnoid haemorrhage (SAH) in your patient.

The search strategy is described in the corresponding BET in the appendix of this paper. The search strategy was repeated in April 2007 to seek additional papers.

Search Outcome

167 papers were found in the search. Six relevant papers have been listed in the original BET and a further two papers found in the repeat search have been considered.

The original BET contained data from five retrospective studies and one review article. These papers reported a sensitivity of 91-98% for the detection of SAH by CT scan. Boesiger et al looked at 177 patients with a suspected diagnosis of SAH. All of the patients underwent CT scan and lumbar puncture. 6 patients had a positive LP and CT scan and there was one false positive CT scan. Coats & Loffhagen performed a literature review and applied Bayesian analysis to the data. They concluded that 1000 patients with negative CT scans would be required to undergo LP in order to diagnose one patient with SAH.

Comments

Emergency physicians need to know if CT is sensitive enough to rule out the diagnosis of subarachnoid bleeding in patients presenting with severe headache. SAH is an important diagnosis to make, the risk of re-bleeding is high if the initial bleed is missed and it is a condition for which treatment is possible. We must therefore err on the side of caution and seek investigations with a very high sensitivity to rule out the diagnosis. The use of LP as a gold standard in many of these studies can be questioned as it too has a false negative rate, particularly when performed soon after a bleed. The diagnosis of SAH is so important that sensitivity must approach 100% for CT to obviate the need for LP. The current trials found reveal 2 interesting facts. 1. That CT has a high sensitivity (91-100%) for detecting SAH, though this is not high enough to satisfactorily exclude SAH. 2. That the sensitivity of CT for SAH decreases with time.

The overall sensitivity given in these trials is not high enough to rule out subarachnoid hemorrhage. The CT is more sensitive, the earlier it is performed which is the converse of
LP. The advantage of CT is that it is quick and easy to perform, may be positive in the early stages of SAH and it may also give information on the cause or size of the bleed. It may also exclude a space occupying lesion.

As CT scanner technology continues to advance the sensitivity of the test is likely to approach 100% obviating the need for LP in patients with a negative scan. In applying Bayesian analysis it is likely that radiological investigation of headache is being offered more widely and therefore the pre-test probability of SAH is likely to be reduced. CT angiography may also have a role to play in the future.

**Clinical bottom line**

Patients with lone acute severe headache should have urgent CT; if this is negative then a lumbar puncture should be performed.

**Recommendation**

In patients with suspected SAH and a negative CT scan lumbar puncture is necessary to exclude the diagnosis.

Grade B recommendation based on level 2a and 2b studies.
8.2 CT Angiography for Detection of Subarachnoid Haemorrhage

Three part question

In [patients with clinical suspicion of subarachnoid haemorrhage] is [CT Angiography better than non-contrast CT and lumbar puncture] in [detection]?

Clinical scenario

A 41-year-old man comes to the Emergency Department complaining of sudden onset of excruciating headache with photophobia and episodes of vomiting. He is a-febrile and has a blood pressure of 180/110mmHg. You are worried he may have a subarachnoid haemorrhage and arrange an urgent CT scan. The scan is reported as showing no haemorrhage. You wonder whether LP could have been avoided by doing a contrast enhanced scan or a CT angiography.

The search scenario is detailed in the corresponding BET in the appendix of this paper.

Search outcome

304 papers were found. One study was considered relevant to this question.

Carstairs et al looked at 131 patients with suspected SAH presenting to one hospital over a 2y period. All patients had a non-contrast CT scan followed by CT angiography (CTA). Patients with a negative CT scan then underwent lumbar puncture (LP). If the CT or LP was positive the CTA result was made available to the receiving neurosurgeon. 1 patient had positive non-contrast CT and a positive CTA. 2 patients had a negative CT but positive LP and CTA. 3 patients had a positive CTA but negative CT and LP. 2 of these patients had aneurysms on normal digital subtraction angiography (DSA) and one patients result was deemed a false positive after negative DSA.

Comments

CT scans are an extremely useful investigation in patients with suspected SAH. However, it is possible to fail to identify small haemorrhages that are obscured by artifact or bone and the process does depend on the expertise of the radiologist. Lumbar puncture for a negative non-contrast head CT is mandatory to rule out subarachnoid haemorrhage in patients with a clinical suspicion of the same. The procedure is time-consuming, unpleasant for patients, can be technically difficult and is not without risks of complication. If CT angiography is found to be effective, it could improve the diagnostic power of CT and reduce or remove the need for lumbar puncture. One problem with carrying out CTA in patients is that it may pick up on incidental aneurysms that exist in around 2% of the population but may not necessarily be causing the patients symptoms. A systematic review by Rinkel et al (1998) has suggests that aneurysms found during investigation of symptomatic patients have a relative risk of rupture of 8.3 compared with patients who have aneurysms found as an incidental finding while being investigated for other conditions. A further potential benefit of CTA is that it may improve the diagnosis of other conditions such as venous sinus thrombosis and AV malformation that may also present as severe headaches.

Clinical bottom line

Only one small study was found comparing CT angiography with non-contrast CT and lumbar puncture for diagnosis of a subarachnoid haemorrhage. Although the results of this study are encouraging the management of suspected SAH cannot be altered on the basis of so few patients. It remains an interesting area for further research.
**Recommendation**

There is insufficient evidence to advocate the use of CT angiography for investigation of suspected SAH.

There is level 3a evidence available.
8.3 Timing of lumbar puncture in suspected subarachnoid haemorrhage

Three part question

[In patients with suspected SAH but a negative CT scan] is [late LP (>12 hours) better than early LP] at [definitely diagnosing SAH]?

Clinical scenario

A 24 year old man presents to the emergency department (ED) with a sudden, severe occipital headache. He collapsed at the time of the initial headache but now feels better. He had a CT scan performed in the ED which was negative. He was subsequently referred to the medical team who performed a negative lumbar puncture (LP) 1 hour after admission (2 hours after the initial headache). This was negative and he was allowed home. One week later he represents to the ED by ambulance following another collapse. He is GCS 3 on arrival and dies shortly afterwards. CT and postmortem reveal the cause of death to be subarachnoid haemorrhage. You wonder if the LP was done too early to spot the original bleed.

The search strategy is given in the original BET.22 The search was repeated in April 2007 for Medline and EMBASE via the Ovid interface.

Search outcome

142 papers were found on the original search of which one was relevant to the clinical question. The repeated search found 245 papers but did not find any additional, relevant papers.

The single paper found was a review article by the UK National External Quality Assessment Scheme for Immunochemistry Working Group.23 The recommendations were based on the fact that formation of bilirubin takes 9-15 hours following a bleed and that bilirubin is the only product of cell lysis that occurs solely in vivo.

Comments

It is common practice to withhold LP until 12 hours following the headache onset. This is based on limited evidence from a small number of papers in this review. Most of the patients in the studies of bilirubin biokinetics had positive CT scans. As LP is normally reserved for those patients with a negative CT scan they are arguably a different group. Despite these limitations current laboratory work suggests that bilirubin may remain undetectable until 12 hours after symptom onset. This should remain the current practice.

What is not shown from the literature is that any patient who had negative initial findings (on early LP) followed by positive findings (on late LP). Such cases would provide a convincing argument, but none were found.

Recommendation

Lumbar puncture is not adequate to rule out a SAH until 12h following the onset of headache.

Grade C recommendation based on a level 3b study.
8.4 Bed rest after lumbar puncture

Three part question

In [patients undergoing diagnostic lumbar puncture] does [a period of bed rest] reduce [the incidence of headache or other complications]?

Clinical scenario

A 27 year old woman attends the emergency department with a two day history of headache with mild neck stiffness. She appears otherwise well. Her CT scan is normal and you feel that if a lumbar puncture is normal she can be discharged. The duty physician advises you that the patient will require four hours bed rest after the lumbar puncture. The duty anaesthetist overhears and says that the patient will be able to go home immediately. You wonder if either of them is right.

The search scenario is detailed in the corresponding BET in the appendix of this paper.

Search outcome

238 papers were found. One Cochrane review was found which looked at data from 14 papers and mentioned 8 other papers that had been excluded. Another systematic review (Thoennissen, 2001) included 11 papers that were in the Cochrane review, 2 papers that were excluded by the Cochrane review and a further 3 papers not mentioned in the Cochrane review. In addition 2 papers were found that had been published after the systematic reviews. One relevant paper was found from before 2001 that was not included in either of the review papers and a further controlled trial that was excluded by the Cochrane review (as not randomised) has been listed here.

Carbaat et al studied 100 patients undergoing investigative lumbar puncture (LP). This was a controlled trial with 50 patients being asked to mobilise immediately and the remaining patients being asked to rest for 24. There was no significant difference in the incidence of headache.24

Vimala et al undertook a RCT in 204 patients undergoing diagnostic LP. 100 patients remained ambulant, while 104 had a 24h period of bed rest. While there was no significant difference in the incidence of headache, the ambulant patients were significantly more likely to report a severe headache than the resting patients.25

Thoennissen et al undertook a systematic review incorporating 2211 patients from 16 trials. 1083 patients were assigned to immediate mobilisation or a short period of bed rest and 1128 patients were assigned to a prolonged period of bed rest. There was no significant difference in the incidence of headache.26

Sudlow et al undertook a systematic review for Cochrane examining the outcome for 1723 patients from 11 trials comparing either bed rest with immediate mobilisation or bed rest for a shorter period of time versus bed rest for a longer period with the primary outcome of headache. There was no significant difference.27

Two further RCTs, published following both systematic reviews, with one looking specifically at paediatric patients, also failed to demonstrate any benefit from a period of bed rest following dural puncture.28 29
Comments

Two systematic reviews and three individual studies looking at this question do not find any benefit for prolonged bed rest following dural puncture. In fact, there was a non-significant tendency for prolonged bed rest to increase the incidence of headaches. The included studies deal with patients who are having dural puncture for different reasons, broadly speaking, diagnostic tests, anaesthetic and myelography. Not only did these patients have different underlying pathologies but they are very heterogeneous groups, some being patients undergoing gynaecological procedures while others were being investigated for suspected meningitis. Despite these facts there was no obvious benefit to prolonged bed rest in any of the groups who were looked at. Publication bias is unlikely to be an issue in this search as one would expect studies showing clear evidence of a benefit of the intervention to be published preferentially.

Clinical bottom line

Bed rest does not decrease the incidence of post lumbar puncture headache.

Recommendation

Bed rest is not necessary following lumbar puncture.

Grade A recommendation based on level 1b evidence.
8.5 Reinsertion of the stylet prior to needle removal in LP

Three part question

In [patients undergoing diagnostic lumbar puncture] does [reinsertion of the stylet prior to needle removal] [reduce the incidence of post-lumbar puncture headache]?

Clinical scenario

A 31-year-old female presents to the emergency department with a sudden onset severe headache. After a normal head CT, you prepare for lumbar puncture with a small gauge non-traumatic needle. You remember a colleague telling you it is also important to replace the stylet before removing the needle in order to prevent a post-lumbar puncture headache. You wonder if there is any evidence is available to confirm this.

The search strategy is documented in the corresponding BET. The search was repeated in April 2007.

Search outcome

235 papers were found in the search. Only one paper addressed the three part question.

Strupp et al prospectively randomised 600 patients undergoing diagnostic lumbar puncture to reinsertion or no reinsertion of the stylet prior to needle removal.\(^{30}\) 49/300 patients had post-lumbar puncture syndrome (headache, tinnitus, dizziness) in the nonreinsertion group vs. 15/300 in the other group.

Comments

The theory is that when CSF is removed, strands of arachnoid enter the needle. When the needle is removed, the strand may then be threaded back through the dural defect and produce prolonged CSF leakage resulting in the post-lumbar puncture syndrome. This was postulated on the observation that the postlumbar puncture syndrome is much lower after spinal anesthesia than after diagnostic lumbar puncture. Replacing the stylet would then push out or cut off any strand of arachnoid. The authors also rotated the needle 90 degrees prior to removal. This is the only study performed looking at replacing the stylet. Some aspects of the study are not clearly described – randomisation, intensity scale, follow up. Nevertheless, there appears to be minimal risk and likely benefit in replacing the stylet prior to removing the needle.

Recommendation

Replacing the stylet before removal of the needle following LP may reduce the incidence of post-LP headaches.

Grade C recommendation based on level 2a study.
9.1 Does Nimodipine reduce mortality and secondary ischaemic events after subarachnoid haemorrhage?

Three part question

[In patients with proven subarachnoid haemorrhage] is [Nimodipine better than placebo] at [in mortality and neurological sequelae]?

Clinical scenario

A 24 year old man presents to the emergency department following sudden headache and an episode of collapse. He presents with a GCS of 13 and a weakness of the left side. CT scan confirms a subarachnoid bleed. You refer him to the neurosurgeons who suggest starting him on nimodipine to reduce cerebral vasospasm. You are too embarrassed to ask why.

The search strategy is described in the corresponding BET in the appendix of this document. The search was repeated in April 2007 across Medline, EMBASE and Cochrane Database of Systematic Reviews via the Ovid interface.

Search outcome

One paper, a Cochrane Review, was found on the original search and found to be relevant to the clinical question. On the repeat search the Review had been updated. No other relevant papers were found.

The systematic review consisted of 2844 randomised patients recruited over 12 trials. The administration of a calcium antagonist was found to reduce the risk of poor outcome, vasospasm and rebleeding with a low risk of adverse effects.

Comments

SAH is a devastating illness. Treatment with calcium antagonists appears to offer a decrease in secondary ischaemic events in these patients. This is shown by the reduction in mortality and clinical findings. Although not specifically addressed in the BET, oral nimodipine appears to be the first choice of drug.

Recommendation

Nimodipine is recommended as treatment for SAH.

Grade A recommendation based on a level 1b study.
9.2 The use of statins for prevention of vasospasm in patients with subarachnoid haemorrhage

Three-part question

In [a patient with a subarachnoid haemorrhage caused by a cerebral aneurysm confirmed by angiographic imaging] are [statins and conventional therapy better than just conventional therapy] in [preventing cerebral vasospasm and delayed ischaemic deficits]?  

Clinical scenario

A 54-year-old male presents to the emergency department with a sudden onset occipital headache, vomiting, photophobia and confusion. A diagnosis of subarachnoid haemorrhage is confirmed by computer tomography. The neurosurgical registrar on-call advises you to start nimodipine and a statin to reduce the risk of the patient developing ischaemic deficits secondary to vasospasm. Is there any evidence to support the use of statins in this situation?

The search scenario is detailed in the corresponding BET in the appendix of this paper.

Search outcome

68 studies were found. Two randomised controlled trials (RCT) were considered to provide best evidence relevant to this question.

Tseng et al performed a RCT in which patients with SAH were randomised to receive either 40mg pravastatin or placebo in a double-blind fashion. Patients received the treatment within 72h of the ictus and continued for 14 days or until discharge. The incidence of vasospasm was measured on a daily basis by Trans- Cranial Doppler (TCD) scan. 17/40 patients receiving pravastatin had vasospasm versus 25/40 patients receiving placebo. 2/40 patients receiving pravastatin died during the study period versus 12/40 patients receiving placebo.33

Lynch et al performed a similar RCT with 19 patients receiving simvastatin and 20 patients receiving placebo in a double-blind fashion. Vasospasm was defined as clinical impression of a delayed ischaemic deficit in the presence of a confirmatory radiological test (TCD or angiogram). 5/19 patients receiving simvastatin were considered to have vasospasm versus 12/20 patients receiving placebo.34

Comments

There is a certainly evidence to suggest that statins have a tendency to protect against delayed ischaemic deficits associated with vasospasm following subarachnoid haemorrhage. Both randomised controlled trials had small numbers involved meaning that they weren’t powered to look at clinical outcome and the follow up the patients was for a relatively short period of time so it is not clear if the beneficial effects would continue. The larger study was carried out in a neurosurgical centre and so concerned a selected population of the patients who present to the Emergency Department with SAH. Statins are only available in oral form so would not be of benefit to the patient with impaired swallowing. There were three retrospective cohort studies looking at patients who presented with SAH who were on long-term statins. 2 of the papers (Parra et al 200435, McGirt et al 200636) found a beneficial effect while the other (Singhal et al, 200537) found an increased risk of a focal neurological deficit or decline in consciousness. These papers have the inherent problems associated with retrospective cohorts in that the patients were on different doses of different drugs for different
periods of time so it is difficult to draw conclusions about commencing this treatment in patients who have had a SAH. Larger randomised clinical trials are clearly warranted but will require a multi-centre study in view of the small numbers of patients admitted to each unit. Given the benefits shown by starting statins early following acute myocardial infarction it may be wise to commence the study while the patients are in the Emergency Department rather than waiting until the patient is received onto the neurosurgical unit. None of the patients in these studies had any adverse effects reported which could be attributed to this class of drugs but there are recognised side effects including myositis and altered liver function.38

**Clinical bottom line**
2 small studies have shown that commencing statins causes a reduction in vasospasm, as measured by TCD, over a 14 day period and a tendency to improve clinical outcome. Local advice following discussion with the neurosurgical team should be followed.

**Recommendation**
There is insufficient evidence to advocate commencing a statin drug in a patient with SAH in the Emergency Department.

There is level 2a evidence available.
9.3 Is the administration of mannitol indicated in patients with confirmed subarachnoid haemorrhage?

Three part question

In [patients with confirmed subarachnoid haemorrhage and raised intracranial pressure] does [the administration of mannitol] reduce [morbidity and mortality]?

Clinical scenario

A 46 year old female presents to the emergency department. A CT confirms subarachnoid haemorrhage On examination there are signs that she has raised intracranial pressure and her clinical condition is deteriorating. You ask one of your colleagues if you should administer mannitol. Neither of you are sure what to do as you have both heard that it is important to maintain cerebral blood pressure fairly high to prevent re-bleeding. However, you wonder if the administration of mannitol would help this patient.

The search scenario is detailed in the corresponding BET in the appendix of this paper.

Search outcome

206 studies were found from the search. None of the papers were felt to answer the question directly.

Comments

No papers found were specific to the original question. Papers are available documenting the use of mannitol intra-operatively\textsuperscript{39,40} for the management of SAH and there is one case report suggesting benefit in 3 patients when combined with dopamine induced hypertension and large volumes of intravascular fluid\textsuperscript{41} but there are no trials looking at its use in these patients in the Emergency Department setting. There are theoretical benefits of giving mannitol to patients with SAH as it has been shown to reduce intracranial pressure and may act as a radical scavenger, decreasing ischaemic injury. There are also known side effects such as cardiopulmonary oedema and rebound cerebral oedema.

Cochrane reviews looking at the use of mannitol in patients with raised ICP due to stroke or head injury have not found compelling evidence of benefit although its use is widespread in the UK & US in patients with head injury.\textsuperscript{42,43}

Clinical bottom line

There is no evidence of benefit of the administration of mannitol in patients with subarachnoid haemorrhage. However, in patients with signs of rising intracranial pressure and decreasing neurological function the benefits may be felt to outweigh the risks. Neurosurgical advice should be sought and followed.

Recommendation

There is insufficient evidence to advocate the administration of mannitol in patients with subarachnoid haemorrhage.

No evidence was found.
9.4 Antifibrinolytics for the initial management of subarachnoid haemorrhage

Three part question

[In patients with confirmed SAH] are [anti-fibrinolytics better than placebo] at [reducing re-bleeding, improving survival or improving morbidity]?

Clinical scenario

A 24 year old man presents to the emergency department following a sudden headache and collapse. He is GCS 14 on arrival with no localising signs. CT scan demonstrates a subarachnoid haemorrhage. In a previous hospital you were advised to give tranexamic acid to prevent re-bleeding. You suggest this to the neurosurgical SpR on call who thinks you are talking rubbish and strongly advises against it. You wonder if he is an evidence-based neurosurgeon ....or whether he is behind the times?

The search is detailed in the corresponding BET.44

Search outcome

267 references found including one recent Cochrane Review. No papers were found after the publication of the Cochrane Review. The search strategy was repeated in April 2007 and no further studies were found.

The Cochrane Review detailed 9 trials involving 1399 patients who had confirmed SAH and had received oral or intravenous agents. There was no significant difference in terms of poor outcome (death, persistent vegetative state or severe disability), hydrocephalus or death alone. There was a decreased risk of rebleeding but an increased risk of cerebral ischaemia.45

Comments

Re-bleeding from subarachnoid aneurysm is thought to be due to local dissolution of the clot by fibrinolytic agents. Antifibrinolytic agents are therefore intended to reduce the risk of re-bleeding and hence reduce the associated morbidity and mortality. A well constructed review article answers the question. Although there appears to be a reduction in the rate of re-bleeding this is not matched by an improvement in patient outcome. The authors of this review postulate that the increase in cerebral ischaemia seen in most of the trials may account for this. From a clinical perspective there appears to be little to be gained from the administration of anti-fibrinolytics in confirmed SAH.

Recommendation

Anti-fibrinolytics are not indicated in the emergency management of subarachnoid haemorrhage.

Grade A recommendation based on level 1b studies.
10. MANAGEMENT ALGORITHM

Emergency Department
Lone Acute Severe Headache

Name____________________

Conscious level

Clinical Risk Assessment

GCS < 15

GCS 15

CT Brain

SAH

Other reason for admission

Lumbar puncture

Xanthochromia

Emergency Treatment

Neurosurgical opinion

Transfer required

No transfer

Therapy advice - overleaf

Complete Ref/045 overleaf

Transfer required

Complete Ref/044 overleaf

Normal

No

Yes

Wait 12 h after onset

Complete Ref/042 overleaf

High

Not high

Complete CDU/041 overleaf

Need for immediate IPPV

Yes

No

Complete Ref/040 overleaf

Patient with Lone Acute Severe Headache

MTS Headache

Discharge for GP follow up

Acute Medical admission

Neurosurgical transfer

Complete Ref/043 overleaf

Guideline for the Management of Lone Acute Severe Headache 22
<table>
<thead>
<tr>
<th><strong>PDI/040: SUITABILITY FOR PROTOCOL DRIVEN INVESTIGATION (ALL YES)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset (thunderclap) headache</td>
</tr>
<tr>
<td>Not previously diagnosed as benign by Neurologist</td>
</tr>
<tr>
<td>Order: T, P, R, BP, SpO₂, U&amp;E, Glucose, Clotting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CDU/041: NEED FOR IMMEDIATE IPPV (ANY YES)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway compromise</td>
</tr>
<tr>
<td>Inadequate respiration (bradypnoea, hypoxia, significant hypercapnia)</td>
</tr>
<tr>
<td>GCS ≤8/15 (consider if GCS&lt;12)</td>
</tr>
<tr>
<td>Hypoxia (SaO₂&lt;92% on supplemental O₂ or pO₂&lt;8 kPa)</td>
</tr>
<tr>
<td>Hypercarbia (pCO₂&gt;5.5 kPa)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CDU/042: CLINICAL RISK ASSESSMENT OF LONE ACUTE SEVERE HEADACHE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Worst headache ever</td>
</tr>
<tr>
<td>Previous SAH</td>
</tr>
<tr>
<td>Fits</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
</tr>
<tr>
<td>Neck stiffness</td>
</tr>
<tr>
<td>Focal neurological signs</td>
</tr>
<tr>
<td>None of the above</td>
</tr>
<tr>
<td>Any H then high risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MEDICAL THERAPY ADVICE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>If GCS&lt;8: Perform and document rapid neurological examination. Perform rapid sequence intubation. Proceed to CT scan asap.</td>
</tr>
<tr>
<td>GCS 9-11: Consider RSI prior to transfer to CT.</td>
</tr>
<tr>
<td>GCS 12-14: Prepare for RSI. Ensure staff competent in advanced airway management available.</td>
</tr>
<tr>
<td>Medical therapy: Nimodipine is of benefit only in proven SAH. The use of mannitol and other agents to lower ICP may be required. Antifibrinolytics (e.g. tranexamic acid) are NOT indicated.</td>
</tr>
<tr>
<td>Lumbar puncture: Bed rest is not needed after LP. Reinsert needle before removing cannula.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>REF/043: SUITABLE FOR DISCHARGE (ALL YES)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Self caring and adequate social support</td>
</tr>
<tr>
<td>Normal CT scan</td>
</tr>
<tr>
<td>Normal LP 12 hours after symptom onset</td>
</tr>
<tr>
<td>Follow up arranged with GP or OPD</td>
</tr>
<tr>
<td>Discharge information given to patient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>REF/044: SUITABLE FOR ACUTE MEDICAL ADMISSION (ALL YES)</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>REF/045: NEUROSURGICAL TRANSFER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess need for ventilation (if not already)</td>
</tr>
<tr>
<td>Ensure staff skilled in advanced airway management conduct transfer</td>
</tr>
</tbody>
</table>
1. Acute Onset of Headaches Require Investigation
2. Does a normal CT scan rule out a subarachnoid haemorrhage?
3. CT Angiography for Detection of Subarachnoid Haemorrhage
4. Timing of lumbar puncture in suspected subarachnoid haemorrhage
5. Bed rest after lumbar puncture
6. Reinsertion of the stylet prior to needle removal in LP
7. Does Nimodipine reduce mortality and secondary ischaemic events after subarachnoid haemorrhage?
8. The use of statins for prevention of vasospasm in patients with subarachnoid haemorrhage
9. Is the administration of mannitol indicated in patients with confirmed subarachnoid haemorrhage?
10. Anti-fibrinolytics for the initial management of subarachnoid haemorrhage
Table 1: Acute Onset of Headaches Require Investigation

Search Strategy:
Conducted in April 2007 of CINAHL, EMBASE and MEDLINE through OVID interface.

[a abrupt.mp. OR sudden.mp. OR thunderclap.mp. OR warning.mp. OR sentinel.mp.] AND [headache.mp.] LIMIT to humans and English.

<table>
<thead>
<tr>
<th>Author, date &amp; country</th>
<th>Patient Group</th>
<th>Study Type</th>
<th>Outcomes</th>
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<th>Study Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linn, F; Wijdicks, E; et al 1994, Holland</td>
<td>148 patients presenting to 252 GPs with a primary complaint of sudden onset (&lt; 1 minute), severe headache over a 5y period were prospectively recruited</td>
<td>Prospective cohort study examining outcomes</td>
<td>Sub Arachnoid Haemorrhage Positive CT scan in pts with SAH [excludes 4 pts that died prior to investigation]</td>
<td>37/148 patients</td>
<td>Patients in study selected for inclusion by GPs. Not all of the patients had CT scans or LPs done although the follow up of these patients is described in another paper and none of them subsequently had a SAH</td>
</tr>
<tr>
<td>Aygun, D; Bildick, F 2003, Turkey</td>
<td>70 consecutive patients presenting with headache with at least one of the following features: worsening; sudden onset; persistence despite analgesia; alteration of character; associated focal neurology</td>
<td>Examined the clinical warning criteria to see which symptoms suggested significant underlying pathology</td>
<td>Diagnosis for patients with sudden onset [31 out of 70 patients]</td>
<td>31/33 patients</td>
<td>Small numbers but high incidence of significant pathology</td>
</tr>
<tr>
<td>Locker, T; Thompson, C; et al 2006, UK</td>
<td>589 patients presenting to one emergency department with a history of nontraumatic headache over a 14 month period. 558 patients had complete data, up to 3 months follow up</td>
<td>Univariate analysis was done of the clinical features to see how well they predicted the presence of serious pathology. Features which appeared to predict serious pathology were entered into the multivariate analysis</td>
<td>Sudden onset as predictor of serious pathology</td>
<td>Sens=65.6%, Spec=62.4%, PLR=1.74 [1.4-2.17], NLR=0.55 [0.39-0.78]</td>
<td>Not all of the presenting patients had the same investigations i.e. CT scan and/or LP. Although the patients were followed up for 3 months, significant pathology presenting after this time period may have been missed</td>
</tr>
</tbody>
</table>

Diagnosis for patients with sudden onset (31 out of 70 patients) 11 SAH, 1 unruptured aneurysm, 1 abscess, 1 intracranial haemorrhage, 1 AVM, 1 IIH, 14 no pathology found.

Patients with SAH All had acute onset of headache.

Any of selected features as prediction of serious pathology (age >50, sudden onset, neurological abnormality) Sens=97.8%, Spec=36.6%, PLR = 1.54 [1.4-1.71], NLR = 0.06 [0.01-0.43]
Table 2: Does a normal CT scan rule out a subarachnoid haemorrhage?

Search Strategy:
Medline 1966-June 2008 including MEDLINE in progress and other non-indexed citations using the OVID interface on ATHENS

[(exp subarachnoid hemorrhage OR subarachnoid.mp OR subarachnoid haemorrhage.mp) AND (exp cerebrospinal fluid OR spinal fluid.mp OR exp spinal puncture OR lumbar puncture.mp OR xanthochromia.mp) AND (exp tomography, x-ray computed OR CT scan.mp)] LIMIT to human, English and abstracts.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>MacDonald, A; and Mendelow, AD; 1987, Scotland</td>
<td>100 patients with diagnosis of SAH confirmed on angiography in tertiary centre</td>
<td>Retrospective chart review</td>
<td>Sensitivity of CT</td>
<td>99 patients had a CT, of these 20 were normal. Sensitivity=80% (CI=15-25%)</td>
<td>This paper did not specifically address the original question. It is subject to referral bias as only patients in a tertiary centre were examined. The CT scanners used at this time were early models.</td>
</tr>
<tr>
<td>Van der Wee, N; et al, 1994, Netherlands</td>
<td>175 consecutive patients with clinical suspicion of SAH Patients with negative CT then went on to have LP. CT was performed immediately, LP after 12 hours from headache onset</td>
<td>Retrospective chart review</td>
<td>Sensitivity for CT</td>
<td>117 patients had blood on CT. Of the other 58 patients, 2 had positive LP's. Overall sensitivity for CT = 95% (CI=94-98.8%)</td>
<td>Not all patients had an LP If the gold standard is LP findings then some of the CT cases may represent false positives</td>
</tr>
<tr>
<td>Sames, TA ; et al, 1996, USA</td>
<td>181 patients with SAH confirmed by LP, angiography, surgery or autopsy who had a CT prior to definitive diagnosis Only 3rd generation scanners included</td>
<td>Retrospective chart review</td>
<td>Sensitivity at more than 24 hours after symptoms</td>
<td>83.8%</td>
<td>Retrospective design There were 349 patients meeting entry criteria but 92 sets of notes were unavailable for review</td>
</tr>
<tr>
<td>Sidman, R ; et al, 1996, USA</td>
<td>140 patients with a diagnosis of non-traumatic SAH LP findings used as gold standard for diagnosis</td>
<td>Retrospective chart review</td>
<td>Sensitivity of CT more than 12 after symptoms</td>
<td>49/60 had positive CT and positive LP (81.7% sensitivity CI 69.5-90.4%)</td>
<td>Retrospective design</td>
</tr>
</tbody>
</table>

Cont.
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</thead>
<tbody>
<tr>
<td>Lachtaw, RE; et al, 1997, USA</td>
<td>Review article</td>
<td>Review article</td>
<td>Sensitivity of CT</td>
<td>Sensitivity of CT ranges from 95-98%. Sensitivity decreases with time (58% at 5 days, 50% at 1 week)</td>
<td>Original data from studies is not presented. Not a systematic review</td>
</tr>
<tr>
<td>Morgenstern, LB; et al, 1998, USA</td>
<td>107 patients with worst headache ever. Patients with negative CT got LP. Scans were reviewed by 2 neuroradiologists blinded to the LP results. LP findings used as gold standard for diagnosis.</td>
<td>Retrospective case note and radiology review</td>
<td>Number of patients with normal CT but positive LP</td>
<td>2 of 89 patients with normal CT had positive LP's. Sensitivity given at 97.5% (CI : 97.8% - 88.7%)</td>
<td>Retrospective design. Not all patients with positive CT had an LP performed</td>
</tr>
<tr>
<td>Boesiger, B; Shiber, J; 2005, USA</td>
<td>Patients attending one hospital over a year period who presented with headache and had a CT scan and a lumbar puncture to rule out subarachnoid haemorrhage.</td>
<td>Retrospective cohort study to calculate sensitivity of 5th generation CT scanners in order to rule out subarachnoid haemorrhage</td>
<td>Sensitivity of CT</td>
<td>100% (6 patients out of 171 had positive CT scans)</td>
<td>Small number of patients with the target condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity of CT</td>
<td>99.4% (One false positive CT scan)</td>
<td></td>
</tr>
<tr>
<td>O’Neill, J; McLaggan, S; Gibson, R 2005, UK</td>
<td>Patients presenting to one Emergency Department who were sent for a CT scan due to clinical suspicion of subarachnoid haemorrhage over a year period.</td>
<td>Retrospective cohort study</td>
<td>Sensitivity of CT</td>
<td>76% (19 patients out of 25 patients that had the diagnosis of SAH)</td>
<td>Over half the patients who had a negative CT scan did not go on to have lumbar puncture. (15% of patients who did have lumbar puncture had a positive result). CT formed part of the gold standard so cannot calculate specificity.</td>
</tr>
<tr>
<td>Byyny, R; Mower, W; Shum, N; Gabayan, G; Fang, S; Baraff, L 2008, USA</td>
<td>Patients who presented to a tertiary Emergency Department over a three year period who were diagnosed as having a subarachnoid haemorrhage.</td>
<td>Retrospective review to determine the sensitivity of non-contrast CT in patients with headache in diagnosing subarachnoid haemorrhage</td>
<td>Sensitivity of CT in patients with SAH</td>
<td>Sensitivity 93% (95% CI 88 to 97%) - 139/149 patients with SAH</td>
<td>Gold standard included CT scans so can’t calculate specificity. Patients may have had a negative CT scan and not proceeded to lumbar puncture due to contraindications or lack of consent. These patients would not have been included in this study although some may have had subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity of CT in patients with SAH and normal mental status at time of presentation</td>
<td>Sensitivity 90% (95% CI 81 to 95%)</td>
<td></td>
</tr>
<tr>
<td>Cont.</td>
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</table>

Guideline for the Management of Lone Acute Severe Headache
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Perry, J; Spacek, A; Forbes, M; Wells, G; Mortensen, M; Symington, C; Forlin, N; Stiell, I 2008, Canada</td>
<td>All patients ≥16y presenting to 2 tertiary care centres with nontraumatic headache and normal neurological examination who had a CT scan to rule out a subarachnoid haemorrhage and a lumbar puncture if the CT scan was normal. Carried out over 3 year period</td>
<td>Prospective cohort study to calculate the sensitivity and specificity of CT scan ± lumbar puncture when used to rule out subarachnoid haemorrhage. Patients were followed up for a minimum of six months following their attendance</td>
<td>Sensitivity of CT scan ± LP</td>
<td>100% (95% CI 94-100%) No patients out of the 531 negative patients was subsequently found to have SAH</td>
<td>60 patients out of 592 were lost to follow up although as the two hospitals involved in the study contained the only neurosurgical units in the region it is unlikely that these patients did go onto to have a SAH</td>
</tr>
</tbody>
</table>
Table 3: CT Angiography for Detection of Subarachnoid Haemorrhage

Search Strategy: MEDLINE, EMBASE, CINAHL, Database of Abstracts of Reviews of Effects, ACP Journal Club and Cochrane Database of Systematic Reviews via OVID interface 01/08.

SAH (Including Related Terms).OR exp Subarachnoid Hemorrhage/ OR subarachnoid haemorrhage.mp.OR subarachnoid hemorrhage.mp. ] AND [exp Angiography/ or exp Tomography, X-Ray Computed/ or exp Cerebral Angiography/ or CT Angiography.mp ] LIMIT to (english language and humans and "diagnosis (sensitivity)"

<table>
<thead>
<tr>
<th>Author, date &amp; country</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Carstairs, S; Tanen, D; Duncan, T; et al 2006, USA</td>
<td>131 patients with symptoms suggestive of SAH presenting to one hospital over a two year period. Patients were excluded if there was a history of allergic reaction to contrast or iodine, there was a history of reactive lung disease or there was evidence of renal insufficiency. 106 out of 131 patients completed the study</td>
<td>All patients had a plain CT scan of the brain followed by CT angiography. Patients with a negative CT then underwent lumbar puncture. If the CT or LP was positive the CTA result was made available to the receiving neurosurgeon. Otherwise the CTA was reported within 24h. All non-contrast CTs and CTAs were then reread in a blinded fashion by a neurosurgeon and 2 neuroradiologists 3-24 months after the patients initial presentation. Patients followed up for 1y.</td>
<td>Patients with SAH on noncontrast CT</td>
<td>1 patient, CTA also positive</td>
<td>Not clear how long after the onset of pain the LP was performed. Xanthochromia was screened visually rather than using spectrophotometry. Small numbers of positive patients</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>Nijjar, S; Patel, B; McGinn, G; West, M 2007, Canada</td>
<td>243 patients with spontaneous SAH confirmed by CT or LP presenting to 1 institution between January 2000 and June 2005</td>
<td>Retrospective review of data of 243 patients with spontaneous SAH confirmed by CT or LP went on to have CTAs. 201 had a +ve CTA showing acutely ruptured aneurysm. 42 remaining had further imaging i.e. Cather angiogram, MRI/MRA or DSA. Of these 33 were thought to have perimesencephalic haemorrhages, 6 had AV malformation and 1 had a PCA aneurysm. For a subgroup of 171 patients who had Neurosurgery, CTA correctly detected the ruptured aneurysm 170 patients.</td>
<td>Detection of acutely ruptured aneurysm</td>
<td>201/243 had a positive CTA scan for an acutely ruptured aneurysm</td>
<td>The study wasn’t powered. The surgeons weren’t blinded to the preoperative CTA findings. The study really only looks at the efficacy of CTA as a diagnostic tool for picking up acutely ruptured aneurysms as the cause of SAH as CTA looks at vascular anatomy</td>
</tr>
</tbody>
</table>

Detection of acutely ruptured aneurysm when comparing preoperative CTA findings with intraoperative findings | 170/171 CTA correctly detected the ruptured aneurysm |
Table 4: Timing of lumbar puncture in suspected subarachnoid haemorrhage

Search Strategy:
Medline 1966-10/04 using the Ovid interface.

\[(\text{exp subarachnoid hemorrhage OR subarachnoid.mp OR subarachnoid haemorrhage.mp}) \text{ AND (exp cerebrospinal fluid OR spinal fluid.mp OR exp spinal puncture OR lumbar puncture.mp OR xanthochromia.mp}) \text{ AND (time.mp OR tim$.mp})\]
LIMIT to human, English AND abstracts.

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</tr>
</thead>
<tbody>
<tr>
<td>UK National External Quality Assessment Scheme for Immunochemistry Working Group. 2003, UK</td>
<td>Review of current recommendations for clinical biochemists in the UK</td>
<td>Review article</td>
<td>Time for formation of bilirubin in CSF</td>
<td>This occurs 9-15 hours following a bleed</td>
<td>Not systematic review Basic data on which recommendation not given</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Selection of bilirubin as key determinant</td>
<td>Bilirubin is the only product of red cell lysis that occurs solely in vivo</td>
<td></td>
</tr>
</tbody>
</table>

This occurs 9-15 hours following a bleed.
Table 5: Bed rest after lumbar puncture

Search Strategy:
Medline, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, ACP journal club, Database of Abstracts of Reviews of Effects (DARE), Cochrane Controlled Trial Register up to 04/07 using the OVID interface.


<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Carbaat, PA &amp; van Crevel , H, 1981, Netherlands</td>
<td>100 neurological patients undergoing LP all done by same investigator with 18G needle. 50 ambulant, 50-24 hour bed rest</td>
<td>Controlled Trial</td>
<td>Incidence of headache</td>
<td>Ambulant- 38% rest- 36% (NS)</td>
<td>p not stated Small numbers. Not randomised</td>
</tr>
<tr>
<td>Vimala, J et al, 1998, Country not stated but ? India</td>
<td>204 patients undergoing diagnostic LP. 100 ambulant 104 24 hour bed rest</td>
<td>PRCT</td>
<td>Headache considered severe</td>
<td>Ambulant 57% Bed rest 12% (p=0.02)</td>
<td>Randomisation method unclear but possibly highly flawed Discrepancies in needle size and operator experience</td>
</tr>
<tr>
<td>Sudlow, C; Warlow, C 2001</td>
<td>Review of randomised trials comparing either bedrest versus immediate mobilisation or a shorter period of bedrest versus a longer period following lumbar puncture</td>
<td></td>
<td>Presence of headache following dural puncture</td>
<td>319/857 (37%) of patients with bedrest had headache vs. 294/836 (35%) of patients with immediate mobilisation</td>
<td></td>
</tr>
<tr>
<td>Thoennissen, J; Herkner, H; Lang, W; et al 2001, Austria</td>
<td>Systematic review of 16 mobilization controlled trials involving 2211 patients who were assigned immediate mobilization or a short period of bed rest versus no bed rest. 1083 patients were assigned to immediate mobilization or a short period of bedrest and 1128 patients were assigned to a prolonged period of bedrest</td>
<td></td>
<td>Presence of headache following dural puncture</td>
<td>392/1128 (35%) of patients with prolonged bedrest had headache vs. 337/1083 (31%) of patients with early mobilization</td>
<td></td>
</tr>
</tbody>
</table>

Cont.
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</tr>
</thead>
<tbody>
<tr>
<td>Ebinger, F; Kosel, C; Pietz, J; Rating, D 2004, Germany</td>
<td>Patients aged between 2 &amp; 17y who underwent diagnostic lumbar puncture at one of 5 hospitals over an eight month period were eligible. Patients who had idiopathic intracranial hypertension, those receiving intrathecal medication and those who were considered too ill to mobilise were excluded. Patients were asked daily about their symptoms for 4 days following the procedure</td>
<td>111 patients were recruited. The patients were randomised to be free to mobilise immediately following the procedure or to maintain strict bed rest for 24h</td>
<td>Headache following procedure</td>
<td>23/59 (39%) of patients who had a period of bed rest vs. 11/52 (21%) of patients who were allowed to mobilise</td>
<td>No standardisation of lumbar puncture procedure. Assessor not blinded to intervention group</td>
</tr>
<tr>
<td>Tejavanija, S; Sithinamsuwan, P; Sithinamsuwan, N; Nidhinandana, S; Suwantamee, J 2006, Thailand</td>
<td>Patients over the age of 14y undergoing lumbar puncture over a 13 month period at one hospital in Thailand. Exclusion criteria included technically difficult procedures and patients with very severe headaches</td>
<td>Patients were randomised to either early ambulation (&lt;1h) or 6h in a supine position. Patients were followed up for 7 days in hospital or by telephone if discharged</td>
<td>Presence of PDP Headache</td>
<td>6/33 (18%) patients who remained in supine position vs. 5/32 (15.6%) of patients who were randomised to early ambulation</td>
<td>Excluded patients with very severe headaches. Only included Post-Dural Puncture Headaches, defined as bilateral headaches, worse on standing and improved on lying down</td>
</tr>
</tbody>
</table>
Table 6: Reinsertion of the stylet prior to needle removal in LP

Search Strategy:
Medline 1966 to 09/04 using OVID interface and The Cochrane Library, Issue 3, 2004 via the NeLH.


Cochrane: [lumbar] next [puncture]

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Strupp M et al, 1998, Germany</td>
<td>600 neurology patients undergoing diagnostic LP randomly assigned (patient blinded) 300 to stylet replacement before needle removal, other 300 not reinserted. Similar sex and age. Used 21G atraumatic needle</td>
<td>Prospective Randomized Controlled Trial</td>
<td>Post-lumbar puncture syndrome (headache, tinnitus, dizziness) reproducible by position and improved laying down, over 7 days</td>
<td>Not reinserted 49/300 (16%) post lumbar puncture syndrome vs. 15/300 (5%) when stylet reinserted. Post Lumbar Puncture Syndrome was also less severe (2.8 vs. 4.5 scale of 10) if stylet reinserted</td>
<td>Excluded patients with headache prior to LP PLPS intensity scale not clearly defined. Follow up not clearly described</td>
</tr>
</tbody>
</table>
Table 7: Does Nimodipine reduce mortality and secondary ischaemic events after subarachnoid haemorrhage?

Search Strategy:
Medline 1966-01/04 using the Ovid interface.


<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Cochrane Stroke Group, 2002, Netherlands</td>
<td>Papers selected from the Cochrane Stroke Group Trials Register (last searched November 2001), handsearch of two Russian journals (1990-1995), contacted trialists and pharmaceutical companies to identify further studies</td>
<td>Systematic review and metaanalysis</td>
<td>Number of relevant papers (Ca antagonists and SAH)</td>
<td>11 papers with 2804 randomised patients</td>
<td>This is a well performed review article. Much of the data is pooled across 4 different types of Ca antagonists. However, the authors also show that the greatest benefit appears to be when nimodipine is used (as opposed to the other Ca antagonists) and when it is given orally rather than IV.</td>
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<td></td>
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<td>Number of papers specific to nimodipine</td>
<td>8 trials with 1574 randomised patients</td>
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<td></td>
<td></td>
<td></td>
<td>Effect on poor outcome Ca antagonist vs. placebo</td>
<td>RR of 0.82 (0.72-0.93) in favour of Ca antagonists</td>
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<td></td>
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<td></td>
<td>Effect on fatality</td>
<td>RR of 0.89 (0.75-1.06) in favour of Ca antagonists</td>
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<td></td>
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<td></td>
<td>Clinical signs of secondary ischaemic neurological deficit</td>
<td>RR of 0.67 (0.59-0.76) in favour of Ca antagonists</td>
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<tr>
<td></td>
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<td></td>
<td>CT evidence of secondary ischaemia</td>
<td>RR of 0.80 (0.71-0.89) in favour of Ca antagonists</td>
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<td></td>
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<td></td>
<td>Rebleeding after SAH</td>
<td>RR of 0.77 (0.58-1.02) in favour of Ca antagonists</td>
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</tbody>
</table>
### Table 8: The use of statins for prevention of vasospasm in patients with subarachnoid haemorrhage

<table>
<thead>
<tr>
<th>Author, date &amp; country</th>
<th>Patient Group</th>
<th>Study Type</th>
<th>Outcomes</th>
<th>Key Results</th>
<th>Study Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tseng et al 2005, UK</td>
<td>80 patients with acute aneurysmal subarachnoid haemorrhage confirmed by angiography in a tertiary centre were recruited out of 86 potential patients. Vasospasm was defined by daily Trans-Cranial Doppler (TCD) scans that measured the mean flow velocities in the middle cerebral arteries</td>
<td>Patients were randomised in a doubleblind fashion to receive either 40mg pravastatin or placebo within 72h of the ictus and to continue treatment for 14 days or up until discharge</td>
<td>Incidence of vasospasm measured with TCD</td>
<td>17/40 of patients receiving statin vs. 25/40 patients receiving placebo (P calculated by log-rank test =0.006, by Fisher's exact test =0.1165)</td>
<td>Study carried with patients accepted by a neurosurgical unit so does not represent the spectrum of patients with SAH presenting to an emergency department. Surrogate mechanism for measuring vasospasm and only measured once a day. Patients with 'symptomatic vasospasm' were treated with Hypertensive Hypervolaemic Hemodilution which has been shown to reverse vasospasm, not clear how many patients had this treatment and if it was only started after vasospasm had been confirmed by TCD. Small study, not powered to show improvement in clinical outcome. Short time period for study. In the patients receiving statins who had vasospasm the time of onset appeared to be delayed and states in text that these patients had delayed ischaemic deficits following the trial, not clear if patients had stopped taking statins at that point</td>
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</table>
### Table 8 cont.

<table>
<thead>
<tr>
<th>Author, date &amp; country</th>
<th>Patient Group</th>
<th>Study Type</th>
<th>Outcomes</th>
<th>Key Results</th>
<th>Study Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch et al 2005, USA</td>
<td>39 patients with acute aneurysmal subarachnoid haemorrhage presenting to one hospital with 48h of onset of symptoms. Not clear if patients were referred to this unit from other centres</td>
<td>Patients were randomized to receive 80mg simvastatin (19) or placebo (20) in doubleblinded fashion, for 14 days. Assessed for vasospasm by TCD 3 times per week. Primary endpoint of vasospasm defined as the clinical impression of a delayed ischaemic deficit in the presence of a confirmatory radiological test (TCD or angiogram)</td>
<td>Presence of vasospasm</td>
<td>5/19 patients receiving simvastatin vs. 12/20 patients receiving placebo (P=0.03 given in paper by Chi square test, p=0.11 when I attempted calculation)</td>
<td>The definition of vasospasm was not clearly defined relying on a ‘clinical impression of a delayed ischaemic neurological deficit’. A small study not powered to detect a significant clinical difference with no long-term follow-up</td>
</tr>
<tr>
<td>Kramer, AH; Gurka, MJ; Nathan, B; Dumont, AS; Kassell, NF; Bleck; TP. 2008, Canada</td>
<td>A total of 150 patients admitted to one neurosurgical intensive care unit with a subarachnoid haemorrhage due to a ruptured cerebral aneurysm. This was a retrospective study examining outcomes before and after the management of these patients was changed to include the administration of 80mg of simvastatin daily in addition to the standard treatment. Exclusion criteria included patients who were admitted 72h or more following the ictus and patients who deteriorated within 5 days to the point that therapy was withdrawn</td>
<td>Compared clinical and radiographic episodes of vasospasm in these patients and looked at adverse outcomes including death using the Glasgow Outcome Scale. 71 patients received treatment with a statin and 79 patients received standard treatment</td>
<td>Clinical vasospasm</td>
<td>20 (no statin group) vs. 23 (statin group), p=0.34</td>
<td>Retrospective study. Not directly applicable to the emergency department as a selected group of patients who had been admitted to a neurosurgical unit</td>
</tr>
</tbody>
</table>

Delayed infarct | 22 (no statin group) vs. 16 (statin group), p=0.46 |

Poor outcome (GOS 1-3) | 28 (no statin group) vs. 28 (statin group), p=0.61 |
Table 9: Is the administration of mannitol indicated in patients with confirmed subarachnoid haemorrhage?

Search Strategy:
Medline 1966 to July Week 1 2006,
Embase 1980 to 2006 Week 28,
CINAHL 1982 to July Week 2 2006,
Cochrane.

Medline, Embase and CINAHL [(exp Intracranial Aneurysm/ or exp Subarachnoid Hemorrhage/) OR SAH OR ((subarachnoid adj (haemorrhage$ or hemorrhage or bleed$)).mp.)] AND [(exp Mannitol Dehydrogenase/ or exp Mannitol/ or exp Mannitol Phosphates/) OR (mannitol.mp.) OR (osmotic diuretic.mp) OR (osmitrol.mp)] limited to humans and English.

No papers
Table 10: Anti-fibrinolytics for the initial management of subarachnoid haemorrhage

Search Strategy:
Medline 1966-12/04 using the OVID interface.

Medline: {exp Subarachnoid Hemorrhage/ or subarachnoid haemorrhage.mp. or exp Aneurysm, Ruptured/ or SAH.mp} AND {exp Antifibrinolytic Agents/ or antifibrinolytics.mp or exp Tranexamic Acid/ or tranexamic acid.mp or exp Aminocaproic Acids/ or aminocaproic acid.mp or exp 6-Aminocaproic Acid/ or epsilon aminocaproic acid.mp or epsilon aminocaproic acid.mp or antifibrinolytic$.mp}

Cochrane: subarachnoid hemorrhage [all fields] OR subarachnoid haemorrhage [all fields]

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<tr>
<td>Roos YBWEM et al, 2003, Netherlands</td>
<td>9 trials involving 1399 patients included. Papers sourced through electronic and hand searching methods. RCTs of IV or oral agents included. Only confirmed SAH patients</td>
<td>Systematic review and Meta analysis</td>
<td>Poor outcome (defined as death, vegetative state or severe disability)</td>
<td>Non significant. OR of 1.12 (CI 0.88-1.43) for poor outcome with treatment</td>
<td>This is a well researched review. The studies match the clinical problem well. Of 21 trials found only 9 satisfied the quality filter of the authors which suggests some rigour in the approach used). One of the review authors' own study was included in the review</td>
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<td></td>
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<td>Rebleeding at end of follow up</td>
<td>Less with treatment OR=0.55 (CI 0.42-0.71)</td>
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<td>Risk of cerebral ischaemia</td>
<td>Worse with treatment OR=1.39 (CI 1.07-1.82)</td>
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<td>Risk of death</td>
<td>Non significant. OR=0.99 (CI 0.79-1.24)</td>
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<td>Rate of hydrocephalus</td>
<td>Non significant. OR=1.14 (CI 0.86-1.51)</td>
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