Guideline for the Management of Lone Acute Severe Headache

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CONTENTS

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[2]. 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[3]. 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[6]. 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.

3. Epidemiological Data

Lone Acute Severe Headache is the main presenting complaint for 1 – 2% of patients who attend the Emergency Department.[4] Between 1-10% of such headaches may be caused by significant pathology requiring urgent investigation and management.[5 6] 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.

4. Scope

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.

5. Definition of Acute 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. Summary of Recommendations

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.

7. Guideline Recommendations – Selection of Patients

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.[5] The remaining patients were followed up for a median of five years with no further incidence of SAH.[7] 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.[8]

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.[9] 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[10] 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.[11-16] 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.[17] 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.[18]

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 contrastenhanced 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.[19] 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.[20] 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.[21] 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 heterogenous 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.[31] 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.[32] 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 neurosugical 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* 2004[35], McGirt *et al* 2006[36]) found a beneficial effect while the other (Singhal *et al*, 2005[37]) 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 trails 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[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[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. [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

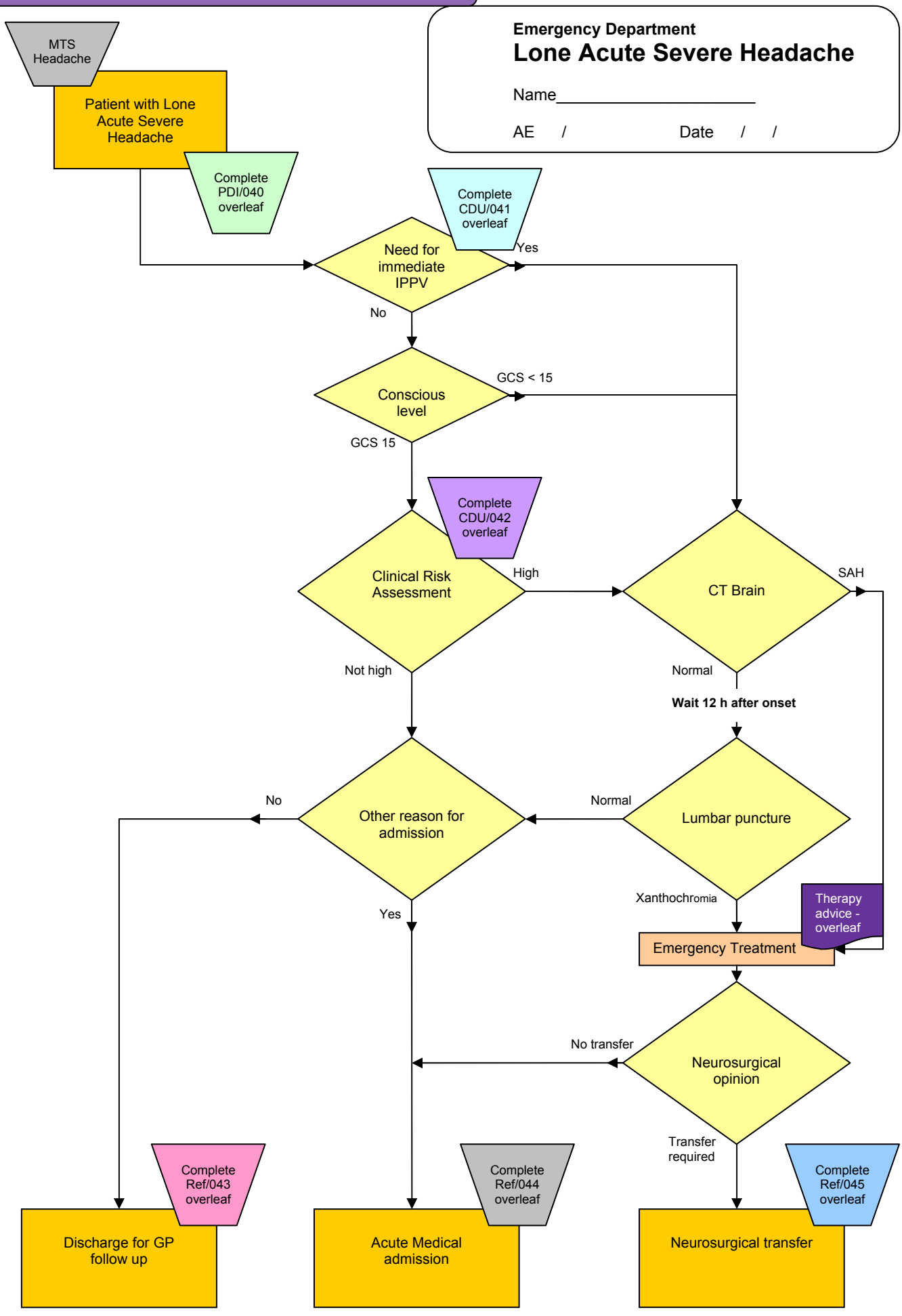
Re-bleeding from subarachnoid aneurysm is thought to be due to local dissolution of the clot by fibrinolytic agents. Antifibrinolytic agents are therefore intended to reduce the risk of re-bleeding and hence reduce the associated morbidity and mortality. A well constructed review article answers the 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



PDI/040: SUITABILITY FOR PROTOCOL DRIVEN INVESTIGATION (ALL YES)

Abrupt onset (thunderclap) headache	Yes
Not previously diagnosed as benign by Neurologist	Yes

Order: T, P, R, BP, SpO_2, U&E, Glucose, Clotting

CDU/041: NEED FOR IMMEDIATE IPPV (ANY YES)

Airway compromise	Yes
Inadequate respiration (bradypnoea, hypoxia, significant hypercapnia)	Yes
GCS ≤8/15 (consider if GCS<12)	Yes
Hypoxia (SaO2<92% on supplemental O2 or pO2<8 kPa	Yes
Hypercarbia (pCO2>5.5 kPa)	Yes

CDU/042: CLINICAL RISK ASSESSMENT OF LONE ACUTE SEVERE HEADACHE

	H	Not H
Vomiting		
Worst headache ever		
Previous SAH		
Fits		
Cranial nerve palsy		
Neck stiffness		
Focal neurological signs		
None of the above		

Any H then high risk

MEDICAL THERAPY ADVICE

If GCS<8: Perform and document rapid neurological examination. Perform rapid sequence intubation. Proceed to CT scan asap.

GCS 9-11: Consider RSI prior to transfer to CT.

GCS 12-14: Prepare for RSI. Ensure staff competent in advanced airway management available.

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.

Lumbar puncture: Bed rest is not needed after LP. Reinsert needle before removing cannula.

REF/043: SUITABLE FOR DISCHARGE (ALL YES)

Self caring and adequate social support	Yes
Normal CT scan	Yes
Normal LP 12 hours after symptom onset	Yes
Follow up arranged with GP or OPD	Yes
Discharge information given to patient	Yes

REF/044: SUITABLE FOR ACUTE MEDICAL ADMISSION (ALL YES)

REF/045: NEUROSURGICAL TRANSFER

Assess need for ventilation (if not already)	Yes
Ensure staff skilled in advanced airway management conduct transfer	Yes

APPENDIX 1: LIST OF BEST BETS

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

APPENDIX 2: SEARCH STRATEGIES AND RELEVANT PAPERS

Table 1: Acute Onset of Headaches Require Investigation

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

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

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Linn, F; Wijdicks, E; *et al* 1994, Holland	148 patients presenting to 252 GPs with a primary complaint of sudden onset (< 1 minute), severe headache over a 5y period were prospectively recruited	Prospective cohort study examining outcomes	Sub Arachnoid Haemorrhage Positive CT scan in pts with SAH (excludes 4 pts that died prior to investigation)	37/148 patients	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
			Positive LP for 2 patients with negative CT scan	31/33 patients	
Aygun, D; Bildick, F 2003, Turkey	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	Examined the clinical warning criteria to see which symptoms suggested significant underlying pathology	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.	Small numbers but high incidence of significant pathology
			Patients with SAH	All had acute onset of headache.	
Locker, T; Thompson, C; *et al* 2006, UK	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	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	Sudden onset as predictor of serious pathology	Sens=65.6%, Spec=62.4%, PLR=1.74 (1.4-2.17), NLR=0.55 (0.39-0.78)	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
			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.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
MacDonald, A; and Mendelow, AD; 1987, Scotland	100 patients with diagnosis of SAH confirmed on angiograpahy in tertiary centre	Retrospective chart review	Sensitivity of CT	99 patients had had a CT, of these 20 were normal. Sensitivity=80% (CI=15-25%)	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
Van der Wee, N; *et al,* 1994, Netherlands	175 consecutive patients with clinical suspicion of SAH Patients with negative CT then went on to have LP. CT was performed immedately, LP after 12 hours from headache onset	Retrospective chart review	Sensitivity for CT	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%)	Not all patients had an LP If the gold standard is LP findings then some of the CT cases may represent false positives
Sames, TA ; *et al,* 1996, USA	181 patients with SAH confirmed by LP, angiography, surgery or autopsy who had a CT prior to definitive diagnosis Only 3rd generation scanners included	Retrospective chart review	Sensitivity at more than 24 hours after symptoms	83.8%	Retrospective design There were 349 patients meeting entry criteria but 92 sets of notes were unavailable for review
			Overall sensitivity	91.2% (CI=87-95%)	
			Sensitivity at less than 24 hours after symptoms	93.1%	
Sidman, R ; *et al,* 1996, USA	140 patients with a diagnosis of non-traumatic SAH LP findings used as gold standard for diagnosis	Retrospective chart review	Sensitivity of CT more than 12 after symptoms	49/60 had positive CT and positive LP (81.7% sensitivity CI 69.5-90.4%)	Retrospective design
			Sensitivity of CT at less than 12 hours after symptoms	80/80 patients had positive CT and positive LP (100% sensitivity CI 95-100%)	
			Overall sensitivity	11/140 (92.1% sensitivity) of patients had normal CT and positive LP	

Cont.

Table 2 cont.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Lachtaw, RE ; *et al,* 1997, USA	Review article	Review article	Sensitivity of CT	Sensitivity of CT ranges from 95-98%. Sensitivity decreases with time (58% at 5 days, 50% at 1 week)	Original data from studies is not presented. Not a systematic review
Morgenstern, LB; *et al,* 1998, USA	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	Retrospective case note and radiology review	Number of patients with normal CT but positive LP	2 of 89 patients with normal CT had positive LP's. Sensitivity given at 97.5% (CI . 97.8% - 88.7%)	Retrospective design Not all patients with positive CT had an LP performed
Boesiger, B; Shiber, J; 2005, USA	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	Retrospective cohort study to calculate sensitivity of 5th generation CT scanners in order to rule out subarachnoid haemorrhage	Sensitivity of CT	100% (6 patients out of 171 had positive CT scans)	Small number of patients with the target condition
			Specificity of CT	99.4% (One false positive CT scan)	
O'Neil, J; McLaggan, S; Gibson, R 2005, UK	Patients presenting to one Emergency Department who were sent for a CT scan due to clinical suspicion of subarachnoid haemorrhage over a year period	Retrospective cohort study	Sensitivity of CT	76% (19 patients out of 25 patients that had the diagnosis of SAH)	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
Byyny, R; Mower, W; Shum, N; Gabayan, G; Fang, S; Baraff, L 2008, USA	Patients who presented to a tertiary Emergency Department over a three year period who were diagnosed as having a subarachnoid haemorrhage	Retrospective review to determine the sensitivity of non-contrast CT in patients with headache in diagnosing subarachnoid haemorrhage	Sensitivity of CT in patients with SAH	Sensitivity 93% (95% CI 88 to 97%) - 139/149 patients with SAH	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
			Sensitivity of CT in patients with SAH and normal mental status at time of presentation	Sensitivity 90% (95% CI 81 to 95%)	

Cont.

Table 2 cont.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Perry, J; Spacek, A; Forbes, M; Wells, G; Mortensen, M; Symington, C; Fortin, N; Stiell, I 2008, Canada	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	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	Sensitivity of CT scan	90.1% (55 positive CTs out of 61 patients with SAH)	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
			Sensitivity of CT scan ± LP	100% (95% CI 94-100%) No patients out of the 531 negative patients was subsequently found to have SAH	

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 haemorrage.mp.OR subarachnoid hemorrage.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)".

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Carstairs, S; Tanen, D; Duncan, T; *et al* 2006, USA	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	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.	Patients with SAH on noncontrast CT	1 patient, CTA also positive	Not clear how long after the onset of pain the LP was performed. Xanthochromia was screened visually rather than using spectophotometry. Small numbers of positive patients
			Patients with negative CT but positive LP	2 patients, both had positive CTA	
			Patients with negative CT and negative LP but positive CTA	2 patients had aneurysms, 1 patient had normal DS angiogram	
Nijjar, S; Patel, B; McGinn, G; West, M 2007, Canada	243 patients with spontaneous SAH confirmed by CT or LP presenting to 1 institution between January 2000 and June 2005	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.	Detection of acutely ruptured aneurysm	201/243 had a positive CTA scan for an acutely ruptured aneurysm	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 anuerysms as the cause of SAH as CTA looks at vascular anatomy
			Detection of acutely ruptured aneurysm when comparing preoperative CTA findings with intraoperative findings	170/171CTA 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.

[(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 (time.mp OR tim$.mp)] LIMIT to human, English AND abstracts.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
UK National External Quality Assessment Scheme for Immunochemistry Working Group. 2003, UK	Review of current recommendations for clinical biochemists in the UK	Review article	Time for formation of bilirubin in CSF	This occurs 9-15 hours following a bleed	Not systematic review Basic data on which recommendation not given
			Selection of bilirubin as key determinant	Bilirubin is the only product of red cell lysis that occurs solely in vivo	

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.

{[exp spinal puncture OR (spinal adj5 tap).af OR (spinal adj5 puncture).af OR (spinal adj5 injection).af OR (lumbar adj5 tap).af OR (lumbar adj5 puncture).af OR (lumbar adj5 injection).af OR (dural adj5 tap).af OR (dural adj5 puncture).af OR (dural adj5 injection).af] AND [exp posture OR posture.af OR supine.af OR flat.af OR immobilis$.af OR recumben$.af OR (bed adj5 rest).af] AND [exp headache OR exp headache disorders OR headache.af]} LIMIT to human AND English Language.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Carbaat, PA and van Crevel , H, 1981, Netherlands	100 neurological patients undergoing LP all done by same investigator with 18G needle. 50 ambulant, 50-24 hour bed rest	Controlled Trial	Incidence of headache	Ambulant- 38% bed rest- 36% (NS)	p not stated Small numbers. Not randomised
Vimala, J *et al,* 1998, Country not stated but ? India	204 patients undergoing diagnostic LP. 100 ambulant 104 24 hour bed rest	PRCT	Headache considered severe	Ambulant 57% Bed rest 12% (p=0.02)	Randomisation method unclear but possibly highly flawed Discrepancies in needle size and operator experience
			Incidence of headache	Ambulant 15% (95% CI 12-22%) bed rest 18% (95%CI 8- 22%)	
Sudlow, C; Warlow, C 2001	Review of randomised trials comparing either bedrest versus immediate mobilisation or a shorter period of bedrest versus a longer period following lumbar puncture	1254 patients from 11 trials reviewed had data available comparing either bedrest with immediate mobilisation or bedrest for a shorter period of time versus a longer period of time with the primary outcome of headache	Presence of headache following dural puncture	319/857 (37%) of patients with bedrest had headache vs. 294/836 (35%) of patients with immediate mobilisation	
Thoennissen, J; Herkner, H; Lang, W; *et al* 2001, Austria	Systematic review of 16 mobilizati controlled trials involving 2211 patients who were assigned immediate mobilization or a short period of bed rest versus a longer period of bedrest	1083 patients were assigned to immediate mobilization or a short period of bedrest and 1128 patients were assigned to a prolonged period of bedrest	Presence of headache following dural puncture	392/1128 (35%) of patients with prolonged bedrest had headache vs. 337/1083 (31%) of patients with early mobilization	

Cont.

Table 5 cont.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Ebinger, F; Kosel, C; Pietz, J; Rating, D 2004, Germany	Patients aged between 2 & 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	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	Headache following procedure	23/59 (39%) of patients who had a period of bed rest vs. 11/52 (21%) of patients who were allowed to mobilise	No standardisation of lumbar puncture procedure. Assessor not blinded to intervention group
Tejavanija, S; Sithinamsuwan, P; Sithinamsuwan, N; Nidhinandana, S; Suwantamee, J 2006, Thailand	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	Patients were randomised to either early ambulation (<1h) or 6h in a supine position. Patients were followed up for 7 days in hospital or by telephone if discharged	Presence of PDP Headache	6/33 (18%) patients who remained in supine position vs. 5/32 (15.6%) of patients who were randomised to early ambulation	Excluded patients with very severe headaches. Only included Post-Dural Puncture Headaches, defined as bilateral headaches, worse on standing and improved on lying down

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.

Medline: [exp spinal puncture OR (spinal adj5 tap).af OR (spinal adj5 puncture).af OR (spinal adj5 injection).af OR (lumbar adj5 tap).af OR (lumbar adj5 puncture).af OR (lumbar adj5 injection).af OR (dural adj5 tap).af OR (dural adj5 puncture).af OR (dural adj5 injection).af] AND [exp headache OR exp headache disorders OR headache.af OR post-lumbar puncture syndrome.mp OR PDPH.mp OR PLPS.mp] AND [needle.mp OR exp needles OR stylet.mp] LIMIT to human AND English language.

Cochrane: [lumbar] next [puncture]

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Strupp M *et al,* 1998, Germany	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	Prospective Randomized Controlled Trial	Post-lumbar puncture syndrome (headache, tinnitus, dizziness) reproducible by position and improved laying down, over 7 days	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	Excluded patients with headache prior to LP PLPS intensity scale not clearly defined. Follow up not clearly described

Table 7: Does Nimodipine reduce mortality and secondary ischaemic events after subarachnoid haemorrhage?

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

[subarachnoid.mp OR exp.subarachnoid hemorrhage] AND [Nimodipine.mp OR exp Nimodipine] LIMIT to human, English AND abstracts.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Cochrane Stroke Group, 2002, Netherlands	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	Systematic review and metaanalysis	Number of relevant papers (Ca antagonists and SAH)	11 papers with 2804 randomised patients	This is a well performed review article. Much of the data is pooled across 4 different types of Ca antagonsits. However, the authors also show that the greatest benefit appears to be when nimpodipine is used (as opposed to the other Ca antagonists) and when it is given orally rather than IV.
			Number of papers specific to nimodipine	8 trials with 1574 randomised patients	
			Effect on poor outcome Ca antagonist vs. placebo	RR of 0.82 (0.72-0.93) in favour of Ca antagonists	
			Effect on fatality	RR of 0.89 (0.75- 1.06) in favour of Ca antagonists	
			Clinical signs of secondary ischaemic neurological deficit	RR of 0.67 (0.59-0.76) in favour of Ca antagonists	
			CT evidence of secondary ischaemia	RR of 0.80 (0.71-0.89) in favour of Ca antagonists	
			Rebleeding after SAH	RR of 0.77 (0.58-1.02) in favour of Ca antagonists	

Table 8: The use of statins for prevention of vasospasm in patients with subarachnoid haemorrhage

Search Strategy:
Search conducted September 2008 of Medline, EMBASE, Cochrane Database of Systematic Reviews & CINAHL.

[SAH.mp OR [subarachnoid.mp AND [hemorrhage.mp OR bleed.mp OR bled.mp OR haemorrhage.mp]]] AND [statin$.mp OR atorvastatin.mp OR cerivastatin.mp OR fluvastatin.mp OR pravastatin.mp OR simvastatin.mp] LIMIT to human and English language.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Tseng *et al* 2005, UK	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	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	Incidence of vasospasm measured with TCD	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)	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
			Mortality	2/40 patients receiving statin, 12/40 patients receiving placebo. (P calculated by log-rank test <0.001, by Fisher's exact test = 0.0064)	

Cont.

Table 8 cont.

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Lynch *et al* 2005, USA	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	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)	Presence of vasospasm	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)	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
Kramer, AH; Gurka, MJ; Nathan, B; Dumont, AS; Kassell, NF; Bleck; TP. 2008, Canada	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	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	Clinical vasospasm	20 (no statin) vs. 23 (statin group), p=0.34	Retrospective study. Not directly applicable to the emergency department as a selected group of patients who had been admitted to a neurosurgical unit
			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:
Medline1966 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.
The Cochrane Library Issue 4, 2004.

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]

Author, date & country	Patient Group	Study Type	Outcomes	Key Results	Study Weaknesses
Roos YBWEM *et al*, 2003, Netherlands	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	Systematic review and Meta analysis	Poor outcome (defined as death, vegative state or severe disability)	Non significant. OR of 1.12 (CI 0.88- 1.43) for poor outcome with treatment	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
			Rebleeding at end of follow up	Less with treatment OR=0.55 (CI 0.42- 0.71)	
			Risk of cerebral ischaemia	Worse with treatment OR=1.39 (CI 1.07- 1.82)	
			Risk of death	Non significant. OR=0.99 (CI 0.79- 1.24)	
			Rate of hydrocephalus	Non significant. OR=1.14 (CI 0.86- 1.51)	

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