Author's response to reviews

Title: Risk factors and clinical presentation of craniocervical arterial dissection: A prospective study.

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Author's response to reviews: see over
Dear Dr Shipley

Thank you for your correspondence regarding the submission of our study protocol MS: 6420026566838194 ‘Risk factors and clinical features of craniocervical arterial dissection’ to BMC Musculoskeletal Disorders. We would like to thank you and your reviewers for the helpful comments which we have now addressed below. The reviewer’s comments are in italics.

The revised manuscript has been uploaded to your website with the changes highlighted in red. A clean copy has also been uploaded.

Reviewer’s report

The authors portray this case-control study as a prospective research design, but in reality it is a case-control design wherein the subjects will be questioned soon after they become cases. The data that is collected will still be retrospective. This methodology, perhaps better termed contemporaneous than prospective, has certain strengths, but it also has weaknesses. For instance, patients interviewed soon after suffering a stroke may be physically and emotionally disturbed to the point that they cannot respond as coherently as someone who has had some time to heal.

We have described the study as a prospective case-control design. We have defined the study as ‘prospective’ based on a definition by Hicks (Hicks 1999) whereby we are prospectively identifying a group of patients we wish to study and will be collecting information from them when they actually present with that condition. The choice of a prospective design is to limit the possibility of selection bias whereby investigators can chose to include participants based on the amount and quality of
information in the medical records. Many previous studies on this topic have utilised a retrospective design or have been a case series, and thereby could have chosen to only include those in whom trauma was identified. We have added a sentence in paragraph 2 of page 3 to highlight this:

‘They may be subject to selection bias if investigators are able to choose whether or not to include individual participants based on information available in their records.’

In our study, participants will be interviewed as close as possible to the time of their stroke in order to minimise recall bias. Importantly, their ability to participate will be determined by their treating neurologist. They would not be interviewed if they were unwell physically or emotionally and if necessary they could be interviewed in the follow up clinic, typically 6 weeks after their discharge from hospital.

The stated purpose of the manuscript is to “…investigate the presenting clinical features and pre-existing health status of CAD patients # 55 years in order to identify risk factors and describe the common early clinical features.” However, too much emphasis is placed on cervical manipulation as a risk factor which may introduce a bias that distorts genuine associations. This reviewer strongly recommends that the manuscript be revised to deemphasize this potential association and weight it the same as the other risk factors.

We respectfully disagree that too much emphasis is placed in this manuscript on cervical manipulation as a risk factor, as it is presented as one example only of minor mechanical trauma. We feel that as there is ongoing controversy about the potential association of neck manipulation with dissection it is important this topic should be specifically explored. However, we have replaced the word ‘manipulation’ with ‘manual therapy’ in the background (p2, para 3, line 1), in order to encompass all aspects of manual therapy to the neck, not specifically manipulation, and removed ‘manipulation’ from para 2 in the Discussion. Two of the investigators are physiotherapists with a particular interest in manual treatment of the cervical spine. However, one of the main purposes of the study is to improve the recognition of CAD by primary care practitioners such as chiropractors, physiotherapists and general practitioners to whom a patient might first present with neck pain or headache. This
is clearly important because as argued by Cassidy et al (Cassidy, Boyle et al. 2008) patients with a dissection in progress may well present to chiropractors, manual therapists or other primary care practitioners for treatment of the related neck pain or headache.

DISCRETIONARY REVISIONS

1) The first sentence, second paragraph on page 2 of the Background section would read better if “which have been undertaken” was deleted, “are” was changed to “were”, and “do” changed to “did”. The next sentence should also be changed as follows: “may include” to “may have included” and the second half of the sentence should be separated into a sentence on its own.

We have made all changes in the 2nd paragraph on page 2 as suggested.

2) The first sentence, third paragraph on page 2 of the Background section is a run-on. Please divide it into 2 or 3 separate sentences.

We have made the recommended change as below:

‘It has been argued that the timely recognition of potential risk factors and more subtle early presenting neurological signs or symptoms of CAD is critical (Debette and Leys 2009; Braun, Tomazic et al. 2011) so that the patient is not exposed to inappropriate manual treatment of the neck. Early recognition is also critical in the case of a patient presenting with a dissection in progress, so that referral for appropriate medical management can be made promptly.’

3) Please delete the first use of “under 55 years” in the section under the heading “Cardiovascular factors” because it is provided below in the list

The first use of ‘under 55 years’ has been deleted.

MINOR ESSENTIAL REVISIONS

1) The first sentence, first paragraph in the Background section on page 1 states that CAD is increasingly being recognized as a major cause of ischemic stroke in younger adults. However, this condition is a well-known cause of
ischemic stroke in younger adults and has been reported in numerous studies over the past several decades so its recognition is not really increasing any more. Thus, please delete “increasingly being recognized”.

We have deleted the words ‘increasingly being recognised’ in the 1st paragraph of the Background section on page 1.

2) The second sentence, second paragraph in the Background section on page 1 is somewhat unclear, because while sometimes CAD post-manipulation is due to inadequate differential diagnosis, the condition often does not manifest symptoms that would lead a prudent practitioner to make that diagnosis. Moreover, CAD is notoriously difficult to diagnose, especially in its early stages when patients are more likely to seek manipulative treatment. Perhaps it would be clearer if the second half of the sentence was replaced with something like this: “…whether some patients already have CAD in its early stages when it is difficult to diagnose.”

We have taken the reviewer’s suggestion to relate the second sentence of the third paragraph of background and amended the wording as suggested.

3) The first sentence, second paragraph in the Background section on page 2 mentions several previous “prospective” studies, but other important studies are missing (e.g., Norris et al and Smith et al immediately come to mind – references listed below). Please consider these studies and search for others as well. Discuss and contrast their work with what you have planned.


We have included the reference for Norris et al’s study in 2000 which is a commentary about cases collected by a network of Canadian stroke physicians. While the study is prospective, it is a commentary on a case series with a focus
on evaluating manipulation as a cause for dissection and therefore may well be open to selection bias.

Smith et al (2003) is a retrospective study, although it did include an interview but this was simply a structured questionnaire administered in most cases by telephone. We consider it is important to interview patients in person as close as possible to their event in order to minimise recall bias. Notably, the authors of this study state that the information obtained was limited by patient recall. The study by Smith et al also did not investigate other potential triggers for dissection such as other types of minor trauma. Moreover, it is unclear whether the sample from which the data were taken was representative of the wider population, as over half the patients meeting selection criteria were unable to be contacted and another 50% of those who agreed to participate were excluded for a variety of reason including incomplete records.

We have included an additional reference (Arnold, Kurmann et al. 2010)

4) Given that this topic has been investigated by a number of researchers using a similar methodology, the authors must provide a rationale and justification for conducting yet another CAD etiology study. Explain what is expected to be discovered that has not already been reported.

The rationale for our study, as identified in the manuscript, is to improve the identification of CAD in its early stages when, as the reviewer points out, it is difficult to diagnose. The unique strength of our study is that we will interview in person patients as soon as medically possible after their dissection. The advantage of this is to limit recall bias and that the medical information obtained will be more meaningful and complete, since it will be obtained closer in time to the event and in consultation with the treating neurologist. Previous studies have interviewed patients at varying times following their dissection, sometimes several years later, and used medical record review and phone interviews as the means of collecting information, excluding patients with limited records. We are also looking at a wide range of risk factors rather than focussing on just one, for example trauma, in contrast to such authors as Norris et al (2000) and Smith et al (2003). We will examine in detail the presenting features, in particular the initial or early neurological signs and symptoms of dissection. Other studies generally
report the clinical features the patient has recorded on admission to hospital, rather than any antecedent ischaemic or other features. It is exactly these features which may aid early and prompt recognition of a dissection in progress by manual or other primary care practitioners.

5) *Cervical spine manipulation is referred to as a type of trauma at several places in the manuscript, but this is actually incorrect. While it has been hypothesized that cervical spine manipulation may be a trigger of CAD, so has backing up a car, watching an airshow, having one's hair shampooed at a beauty parlor, etc., none of which are traumatic events. To put manipulation alongside sports activities that commonly place gross injurious strains on the neck, as well as with direct and indirect trauma is imbalanced and may lead health care providers who provide this type of treatment to needlessly discontinue using it or may prevent other health care providers from referring patients for manipulation. Therefore, I recommend that you explain more about the difference between frank trauma and what has been referred to in the literature as “trivial” trauma and how manipulation fits into the latter category along with other common non-traumatic neck movements.*

Frank trauma has not generally been implicated in dissection. We have added some detail into the background (page 1, para 2, line 12) to explain this. It was not our intention to imply that manipulation was a type of frank trauma and have only listed it as one type of minor or trivial trauma. We have changed the descriptor to ‘*minor* mechanical trauma or activities which impart some stress to the neck’ in the Background section on page 1 in paragraphs 2 and 3 to clarify this. We have also changed the wording ‘manipulation may be a cause for dissection’ to ‘manual therapy’ and added the additional explanation as follows:

“Cervical spine manual therapy has been hypothesised as one type of minor trauma or stress to the neck which may be a trigger for CAD. (Background 1st sentence para 3)

Such minor trauma is usually innocuous, such as might occur during the course of normal daily activities. Frank trauma, such as may happen during a motor vehicle accident has not usually been reported (Norris, Beletsky et al. 2000; Debette, Grond-Ginsbach et al. 2011).” (page 1, para 2, line 13)
6) Please describe the timing of the structured interviews in the Methods section. Will the timing be the same for all participants? Patients may be emotionally charged and/or confused soon after admission which could distort their responses.

Participants will be interviewed as close as possible to the time of their dissection or stroke when they are medically and emotionally stable, and at the discretion of their treating physician. As far as possible the timing will be similar for all participants. In our experience, patients who have suffered dissection are often reasonably able and willing to talk about their experience and preceding events. In the event they were not well enough to be interviewed while in the acute hospital setting they could be interviewed in the rehabilitation ward or in the follow up clinic, usually about 6 weeks post discharge.

7) Please describe how selection bias will be controlled. For instance, who will determine which patients become cases? Will they have access to the patient’s history before deciding whether to accept the patient as a case (i.e., will they be blinded)?

As described in the participant section of the Methods (p5), all patients referred to hospital in the local region with a diagnosis of dissection will be included if they give their consent, which should help to reduce selection bias. The main hospital is a tertiary referral centre so the majority of cases of young stroke in the region would be referred and reviewed there. Participants will be identified by the treating neurologist and stroke research nurses. It is not possible to blind the interviewer as they are an investigator in the study, however they will not have access to the patient’s history before recruiting them into the study. This also should help reduce selection bias.

8) Please indicate who will conduct the structured interviews and describe how they will be trained. Will they have any freedom to deviate from the interview script? I yes, how much freedom? This information is needed in order to assess the probability of interviewer bias.

The structured interviews will be conducted by one of the investigators who is a registered physiotherapist with post-professional qualifications in manipulative physiotherapy, and 28 years of clinical experience working as a manual therapist.
We have added this to the manuscript on page 6, Participant characteristics, line 4.

The interview script is provided as a guide or checklist only in order to ensure all information is covered equally for both cases and controls. The interviewer will be free to follow-up any additional related points which may come up in the history or presentation described by the participants. Accordingly we have changed the word ‘script’ to ‘guide’ in the appendix.

9) The interview script should be written to the level of a person who only graduated from about the 7th grade. The term “palpitations” is used in item 3, which would likely be above that level. In item 6 of the interview script both “difficulty with your speech” and “difficult speaking” are included in the same sentence, which is redundant.

We respectfully disagree with the reviewer that the interview script should be written at a lower level of English as the interview is not intended to be completed by the participant on their own, nor by an interviewer without a health professional background. If the participant does not understand any terms or questions, then the interviewer will provide further or alternate explanations to ensure participant comprehension.

Item 6 in the script is intended to differentiate between a motor control problem: dysarthria (difficulty speaking), and a problem of coordinated expression: dysphasia (difficulty with your speech).

10) Item 7 in the interview asks whether the subject felt nauseous or vomited. Please add “as a result of the dizziness or loss of balance”. Otherwise, patients who respond that they vomited as a result of a migraine, for instance, could distort the resulting data by classifying them as being dizzy.

We have amended item 7 of the interview script to read ‘did this make you feel nauseous or vomit? ‘this’ being in relation to the dizziness or loss of balance. The question is contained within the section on balance disturbance so is intended to apply to this.

11) Item 1 in the Risk factors section of the interview should be reworded. Currently the phrase “have you had done” does not fit with some of the responses below it;
“heavy lifting”, for instance. The section on manual treatment in this section places too much emphasis on these procedures as compared to the other risk factors. This emphasis may be result in it becoming a leading question. As a suggestion, consider using this wording: “Any manual treatment of your neck such as manipulation, forceful neck turning, or deep massage to the top of your neck”.

As recommended, we have changed the section on risk factors as follows:

The sentence containing the phrase ‘have you had done’ includes a typographical error which we have corrected by removing the word ‘had’ page 3, Risk factors point 1, line 1.

‘Any manual treatment of your neck such as manipulation, forceful neck turning, or deep massage to the top of your neck.” Page 3, point 1, line 9

We have also amended the last sentence in this section:

‘Have you ever had any adverse reaction to this type of treatment in the past?’

MAJOR COMPULSORY REVISIONS

1) The second sentence, first paragraph in the Background section on page 1 gives the annual incidence of CAD as 2.5-3:10,000, which is incorrect. It should be 2.5-3:100,000… a ten-fold difference.

We have corrected the incidence figure to 2.5-3:100,000. This was a typographical error and we appreciate the reviewer pointing it out so we could correct it, page 1, para 1, line 5.

2) The second sentence, second paragraph in the Background section on page 1 implies that other authors have indicated that the mechanism of CAD etiology involves both a pre-existing intrinsic susceptibility AND a precipitating event, which is incorrect. Sometimes no discernible event occurs in the progression of CAD. The condition can be and often is completely spontaneous. In fact, this manuscript’s reference 17 indicates that 61% of CADs reported over a 10 year period were spontaneous.

We agree with the reviewer that some dissections appear to be spontaneous, however there has been some debate in the literature (Norris, Beletsky et al.
2000; Debette and Leys 2009) as to whether these cases are truly spontaneous or whether it is just that a trigger has not been identified in that particular case, perhaps due to inadequate history reporting. We have added further detail to paragraph 2 of the Background section on page 1 as follows:

‘The aetiology of CAD is not fully understood and many cases are described as occurring spontaneously when no obvious mechanism or trigger can be identified. However, it has been suggested that for dissection to occur there must be a contribution from both intrinsic and extrinsic factors….’

3) The heading “Mechanical trauma” in the Measurement of risk factors for CAD section on page 6 uses the term trauma inaccurately. Please delete the word trauma altogether or replace it with “actions” or “activities”. The authors may defend their position by citing other researchers who have used the term “trauma” to define this category, but please consider that these other researchers have employed an inaccurate definition as well. Many CAD triggers (i.e., reports of activities that preceded CAD, but were not necessarily causally related) are considered normal activities and therefore should not be categorized as trauma. The same type of inaccuracy in which neck manipulation is represented as “mechanical trauma” occurs in the first sentence, second paragraph on page 9 of the Discussion section. As a suggestion, consider writing something such as: “In the case of recent neck manipulation, the study will allow more detailed information to be gained on the nature of the forces involved and direction of movement of the neck.” The next sentence will have to be reworded as well.

We have addressed this point by adding the descriptor ‘minor’ and ‘activities which impart stress to the neck’ to the Background section on page 1 as discussed previously in point 5 above. We have also changed this in the section on measurement of risk factors now on page 7. We have removed the example of neck manipulation as a type of trauma from paragraph 2 of the Discussion now on page 10.

4) Also under the heading “Mechanical trauma” it indicates that “…If any trauma is reported, specific descriptive details of the amount of force involved and direction of movement of the head and neck will be sought from the
yet there is no provision for this kind of dialogue in the interview script. Please clarify. Also, one must exercise constraint in applying much credence to patients’ descriptions of the vectors that they experienced during cervical manipulation. Please refer to the following study which reported on the difficulties patients had recalling how they were manipulated by a chiropractor. Lewkovich G, Haneline M. Patient recall of the mechanics of cervical spine manipulation. J Manipulative Physiol Ther. 2005;28(9):708-12.

We acknowledge that patient recall and understanding of the specific nature of manipulative treatment is highly likely to be subject to bias and so we will only collect general details such as manipulation, forceful neck turning or massage, as described in the script.

Yours sincerely

Lucy Thomas

References


