This is a report by

Dr Malcolm Coulthard

requested by the *Inquiry into Hyponatraemia-Related Deaths*

in response to the document by Dr L Dyer, 24/01/2012

10/02/2012

Remit

I have been sent a copy of Dr L Dyer's report of 24/01/2012 by the *Inquiry into Hyponatraemia-Related Deaths* team to comment upon.

Were the CVP readings valid?

I am grateful to Dr Dyer for clearly drawing attention to Dr Taylor's statement on 011-002-006, repeated on 011-014-099, that "There were both cardiac and respiratory patterns to the waveform confirming correct intravascular placement." This statement confirms that Adam's CVP reading was indeed a valid measure of the status of his central veins, and that it was not an artificial or spurious reading resulting from obstruction to the veins in his neck, as has been postulated elsewhere.

Dr Dyer is absolutely correct in his "belief that it is mandatory for the clinician to investigate the cause" of such an abnormal finding.

Dr Taylor's next action, which instead was to disregard the CVP as an accurate tool to assist making anaesthetic decisions *because its value was so high*, was an illogical and important mistake. Had he recognised that the CVP genuinely *was* high, he would have been able to consider the possibility that Adam was already well hydrated, rather than believing him to be dehydrated.

The perfusion pressure of a child's brain during anaesthesia in a head-down position.

The absolute intracranial pressure (ICP) is measured in relation to the atmospheric pressure outside the head. This may be measured using a pressure sensitive device (transducer) inserted through a hole made in the skull, and which is calibrated to read zero while it is situated at the same vertical height as the head.

However, if the mean arterial blood pressure (MAP) is measured in the blood stream through a cannula that is connected to a pressure transducer fixed at the level of the heart, then the ICP *relative to that* will depend upon the vertical distance between the heart and the head.

The flow of blood that can be achieved through the brain depends upon a combination of the dilatation of the blood vessels within the brain (how relaxed and open they are, or how narrowly they are held in spasm), and the pressure gradient of the blood driving the perfusion. This pressure gradient is the pressure in the arteries leading to the brain minus the venous pressure, and minus the ICP, and is termed the cerebral perfusion pressure or, CPP. In normal children, the absolute ICP and the pressure of blood in the veins in the chest (the central veins; hence the central venous pressure, or CVP) are negligibly low. They are therefore usually ignored, and it is typically assumed that the CPP equals the MAP.[1]

In a normal subject who was lying flat, the CPP will therefore equal the MAP measured through a blood pressure transducer calibrated to zero at the level of the heart. However, if their head was higher than their heart (eg, they were standing up), this would *decrease* the CPP by that vertical distance, as the heart was having to pump 'uphill'. Thus, if the mid-point of an adult's head was 30 cm above the level of their heart, their CPP whilst standing up would be their MAP – 30 cm water. The MAP is conventionally measured in mm of mercury (mmHg). Since the density of mercury is 14-times that of water, 1 cm of water pressure equates to 1.4 mmHg. The CPP in this case would therefore be about MAP – 21 mmHg.

This is why the blood pressure reflexly increases as people move from lying to standing, to compensate for the fall in CPP as the head is raised above the heart. Most people will be aware of this phenomenon themselves when it is a bit slow to kick in, when they sit up or stand up quickly from

[1] Chambers IR, Jones PA, Lo TYM, Forsyth RJ, Fulton B, Andrews PJD, Mendelow AD, Minns RA. Critical thresholds of intracranial pressure and cerebral perfusion related to age in paediatric head injury. J Neurol Neurosurg Psychiatry, *2006;**77**:234-240.*

lying down. The sudden lowering of the CPP produces a reduced blood flow which may be experienced as giddiness or even blacking out (the syndrome of postural hypotension).

The opposite happens when the head is held below the heart, such as when someone stands on their hands, or when a child is anaesthetised in the head-down position. The *relative* ICP, compared to the MAP at the heart, *increases* by the vertical distance that the head is below the chest. In a child of Adam's size, unless the child was positioned with their neck grossly extended or the operating table was at an extreme tilt, it is unlikely that the vertical mid-point of the brain would be more than at most 15 cm below the level of their heart. Thus, the CPP would be approximately 10 mmHg *greater* than the MAP, and not lower than the MAP, as Dr Dyer argues.

Dr Dyer concluded that the CPP would be 25 mmHg *lower* than the MAP, and that this would reduce the CPP directly. I presume that the figure of 25 must have been estimated from the assumption that the mid-point of Adam's head would have been 25 x 1.4 = 35 cm below the level of his heart, which seems an unlikely vertical distance. Since Adam's MAP was recorded as 75 mmHg at the time of surgery, he concludes that his CPP would have been reduced from 75 to 50 mmHg by being positioned in this manner.

The fact that I have argued that his mean arterial blood pressure at the level of his brain would have been about 10 mmHg *higher* than the MAP at the heart, does not however mean that I am arguing that the CPP would have been increased by his head-down posture. This is because, while the blood pressure applied to the carotid arteries to perfuse the brain is increased by 10 mmHg, so too is the venous return pressure applied to the blood returning to the heart from the jugular veins. That is, while the blood pressure can push blood into the brain easier, the venous pressure resists its return equally hard, and the gradient of blood pressure across the brain remains unaltered.

Thus, whilst the head being held higher than the heart may pose a problem if the blood pressure is insufficient to pump blood high enough[2], it does not alter the arterio-venous pressure gradient, and holding it lower than the heart would not be expected to alter the perfusion of the brain by this mechanism.

The impact of a raised CVP on cerebral perfusion

As noted above,[1] neither the ICP nor the CVP is considered to be an important factor in the CPP of normal children, and this is usually equated in clinical practice merely to the MAP. However, it is self-evident that if the CVP was abnormally high, this could reduce the CPP, by reducing the arterio-venous pressure gradient.

It is standard practice in children undergoing a renal transplant to be deliberately maintained with a normal or slightly over-filled blood volume. This is because the extra amount of blood is needed as soon as the blood supply to the new kidney is connected to the child's circulation, as the donated organ is drained of its own blood during its preparation for grafting. It is therefore normal for children anaesthetised for a transplant to have sufficient extra fluid to increase their CVP by up to about 10 mmHg (see my report of 7/11/2011, page 11 where this is discussed in detail).

This means that the arterio-venous pressure gradient, or CPP, of a child whose MAP was 75 would be reduced to about 65 mmHg as a matter of course during transplant surgery.

After studying Adam's transplant anaesthetic charts, Dr Dyer takes a CVP value of 22 mmHg as being an appropriate figure to consider. Using this value, it can be seen that the CPP would be reduced further in a boy with a MAP of 75, down to 53 mmHg. Thus its impact on Adam should be regarded as a fall from a level of 65 to a value of 53, or a fall of 18%.

Dr Dyer clearly considers that a CPP of 48 mmHg can be considered as a useful "critical threshold" to influence the anaesthetic management of children in Adam's age group.[1] I consider it an over-

[2] The implication of this for giraffes has been extensively studied; they require a much higher blood pressure than do short-necked animals to be able to perfuse their brains while their heads are held high.

interpretation of the literature to quote a single value for neurologically normal children, when it is based on a single (albeit high quality) paper (from my colleagues in Newcastle) of 81 children who had intra-cerebral pressure monitoring following head-injury.

Perhaps of equal relevance is the fact that in my experience of approximately 200 paediatric kidney transplants, in which the CVP was typically maintained in the range of approximately 7 to 10 mmHg, there were many whose MAP was significantly lower than 75 (and who therefore had CPP values as low as Adam's, or lower), and the fact that none sustained cerebral oedema as a result. Tragically, one young child that I managed did die following to a perturbation of his CPP during his transplant anaesthetic, but in his case it was due to his CPP being highly excessive, because his MAP was allowed to reach levels that would have been high for an adult, and which were disastrously high for him.[3]

It is also of note that at the time that Adam was transplanted it was very common, almost the norm, that children were anaemic whilst they underwent their graft surgery. This is because the kidneys play a major role in regulating the blood haemoglobin concentration by producing the hormone erythropoietin, and usually fails to do this in parallel with failing to clean the blood of its waste products (children today receive erythropoietin treatment to prevent anaemia).

In the light of these observations, I suggest that Dr Dyer is incorrect to reach the conclusion (D14) that in Adam case, a MAP of 75, a CVP of 22, and anaemia "combined to make cerebral hypoxia inevitable".

The use of CVP to determine fluid management

In his final conclusions, Dr Dyer introduces a further issue (H6), which is that in his opinion the CVP should not be used to guide fluid management. He expresses concern that CVP is being used in this way despite it being "definitive that it should not".

The single paper that he refers to[4] includes a meta-analysis of the prediction of blood volume from CVP in 230 *adult* patients, of which over half were from just one study. The authors acknowledge that CVP is used almost universally to guide fluid therapy in hospitalized patients, but interpret their results suggest that this may not be as appropriate as is widely held.

Whether or not they are correct about this in adult humans in general, the key point is that older patients being treated in intensive care (as they all were in their study) will between them have a host of pre-existing pathologies, including coronary and pulmonary diseases as well as relatively inelastic blood vessels and other factors that compound the otherwise well described and clearly understood physiological relationship between the CVP and the adequacy of the blood volume. This is not relevant to paediatric practice, where this relationship is known to be reliable in children without specific cardio-respiratory illnesses. In the same way, the authors of this paper acknowledge a clear relationship between CVP and blood volume in healthy animals, which they consider important enough to refer to in the title of their paper.

The fact that CVP *does* reflect the blood volume in children with normal hearts and lungs is why all children's kidney transplant protocols throughout the world advocate using the approach employed both in Newcastle and Belfast. Indeed, in the very rare occasions where this relationship cannot be assumed, special measures would have to be taken.[5]

---

[3] For the record, this led promptly to multidisciplinary discussions, and the introduction of new blood pressure management guidelines which were applied across the whole of the hospital's paediatric disciplines, including paediatric medicine, surgery and anaesthetics. We also disseminated this advice throughout the Northern Region paediatric departments for whom we provide general advice on matters of paediatric nephrology.

[4] Marik PE, Baram M, Bobbak V. Does central venous pressure predict fluid responsiveness? : A systematic review of the literature and the tale of seven mares.

[5] An example of this was a teenager we transplanted with a kidney who had had a heart transplant as a toddler. We then relied upon paediatric cardiology and paediatric cardiothoracic anaesthetic colleagues for extra support. In fact, her clinical CVP-blood volume responses *were* preserved, and in retrospect could have been relied upon.

Summary

I am grateful that Dr Dyer has clarified that Adam's CVP line was working properly, and believes that Dr Taylor should have investigated the cause of the high reading rather than disregarding it as spurious.

It is my view that Dr Dyer's pathophysiological predictions of the impact of anaesthetising a child in a head-down position are wrong, and that this would *not* alter the cerebral blood perfusion pressure.

I agree that a raised CVP would inevitably alter the potential CPP if, as he assumes, that individual child had already used up all its other compensatory mechanisms in every other way. However, I do not consider that this would have been relevant in this case, as even a level as high as 22 mmHg would only effect it in a clinically unimportant way. I reject completely his conclusion that cerebral hypoxia was inevitable in Adam's case because of this. I bring my extensive experience in looking after children during the peri-transplant period to support my position.

I also reject Dr Dyer's strong plea not to use CVP measurements clinically to assess blood volume, as this recommendation against what is an almost universal practice is based on a small study of adults requiring intensive care, and not on children who behave physiologically very differently.

Conclusion

Adam's positioning during his transplant anaesthetic, and his raised CVP were not major factors in his developing cerebral oedema. Instead, this was overwhelmingly due to fluid moving into his brain cells by osmosis as a result of his fluid mismanagement.

Expert Witness Declaration

I Malcolm Coulthard DECLARE THAT:
1) I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.
2) I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.
3) I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4) I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.
5) I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.
6) I have shown the sources of all information I have used.
7) I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.
8) I have endeavoured to include in my report those matt ers, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.
9) I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10) I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11) I understand that;
    11.1) my report will form the evidence to be given under oath or affirmation;
    11.2) questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;
    11.3) the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;
    11.4) the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;
    11.5) I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;
    11.6) I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.
12) I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the "Protocol for Instruction of Experts to give Evidence in Civil Claims" and I have complied with their requirements.
13) I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Signed M.S. Coul Dr Malcolm Coulthard

Dated 10/2/12 10/02/2012

Dr Malcolm Coulthard, BSc, MB BS, DCH, FRCP, FRCPCH, PhD