Annals of Neurosurgery 2009; 9(5): 1-24

The Proceedings of the IVth Annual International Neurosurgery Conference

Part I

www.surgicalneurology.org/conf4
27-30 December 2008

Patron: Mr Owen C Sparrow FRCS
Southampton

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Invited Presentation

Evidence Based Medicine and Neurosurgery

Robert E Harbaugh, MD FACS FAHA [Hershey, Pennsylvania]

Question from Dr J Loeser to Dr RE Harbaugh

Should the NIH stop funding RCTs for neurosurgical interventions?

John D Loeser MD
Seattle

Response of Dr RE Harbaugh to question of Dr J Loeser

John,

I wouldn't make a blanket statement about all RCTs but in general I believe that the expense associated with multicenter RCTs is money spent foolishly. I submit that our reliance upon null hypothesis testing and RCTs has had more negative than positive effects for neurosurgical clinical research. This kind of iconoclastic statement will require a good deal of clarification.

The RCT methodology was developed to address three problems common to clinical research - bias,confounding and chance. To do this, the properly designed RCT has four essential components: concurrent comparisons to

eliminate temporal bias; objective observation of clear endpoints to eliminate physician and patient bias; randomization to equalize the effects of unknown, confounding variables; and a representative, adequately sized patient population to reduce the likelihood of chance errors. The ideal RCT, the adequately powered, double-blind study with unambiguous endpoints, has all of these components. Unfortunately, most surgical RCTs cannot approximate this ideal.

An RCT is performed to determine the presence or absence of a treatment effect. Before beginning the trial, the null hypothesis—a statement that there is no statistically significant difference between treatments—is accepted. In a positive study, the null hypothesis is rejected, indicating a significant difference between treatments. If the null hypothesis cannot be rejected, a negative result, the study concludes that there is not a statistically significant difference between the treatments.

For positive trials the chance that the observed difference was seen, even though the null hypothesis was true, is represented by the P value. A trial with a P value of less than 0.05 tells us there is less than a 5 percent chance that results as different as those observed in the study occurred by chance alone.

For negative studies the power of the study is important. Power is the likelihood of determining a positive result if there is a real therapeutic difference between treatments. Stated simplistically, a study with a power of .80 means that there was an 80 percent chance of finding a difference of a predetermined magnitude if such a difference really existed. The power of a study is dependent on sample size, the magnitude of the treatment effect chosen and the statistical tests employed. Too often we see underpowered studies that report "no significant difference in X" because data showing substantial differences that were rejected as being meaningful because t-testing mean values did not resulted in a p value of 0.08 or 0.14. This is foolishness.

For many clinical studies the well designed RCT is an immensely powerful tool. Consider a double-blind RCT evaluating mortality from myocardial infarction in patients who receive either placebo or aspirin after the event. In this RCT neither the patient nor the investigator know which compound is administered, there are no patients who cross over from one treatment to the other, and the endpoint is unequivocal. If this study is adequately powered it will produce unambiguous results.

Furthermore, if the patient population studied in this RCT is representative of the universal population of patients suffering myocardial infarction, and the trial shows a significantly better outcome with aspirin, then aspirin can be given to myocardial infarction patients with a high degree of assurance that one is delivering quality care.

However, surgical trials differ from this example in several important ways. Because nearly all surgical trials are unblinded, patients may elect to cross over from one treatment arm to another, such as from medicine to surgery. To preserve the benefits of randomization, it is necessary to analyze patients in their assigned groups even if they cross over to another treatment arm (intention to treat analysis). Crossovers create problems in any clinical trial.

In trials comparing medical to surgical treatment the problems are compounded because the crossover periods often are asymmetrical. After assignment to surgery there is a short period of time, preoperatively, during which the patient may elect other treatment. Patients have a comparatively longer time span in which to consider changing from medical to surgical treatment. For example, in a trial comparing surgical to nonsurgical treatment of back pain, the patient who is randomized to medical treatment may try this for weeks or months, have persistent pain, choose to have surgery and then do well. However, the good outcome at follow-up will be assigned to the medical treatment arm; is there anyone who would consider this to be reasonable? Statistical methods exist to deal with crossovers, but these methods ameliorate rather than eliminate the problem.

It is also difficult in many neurosurgical trials to define clear endpoints. A neurosurgical RCT does not eliminate bias if endpoints are ambiguous and neither the patient nor the evaluator is blinded. Patients may experience a substantial placebo effect with surgery and investigators may harbor a surgical or nonsurgical bias. Having someone other than the operating surgeon evaluate patients postoperatively does not solve this problem. Any unblinded observer will bring his or

ther bias to the evaluation.

It is also more difficult in surgical trials to choose a representative patient population because of the problems of therapeutic imperative and equipoise. The surgeon has an implicit contract with the patient to offer the best care available (therapeutic imperative). If the surgeon does not believe that surgical and nonsurgical treatment arms are equally efficacious (equipoise) he or she will offer surgical treatment outside the trial to those patients he or she believes are most likely to benefit. Only those patients less likely to benefit from surgery are randomized, skewing the patient population to the detriment of the surgical treatment arm.

Surgical RCTs also suffer from problems with surgeon selection. In a study comparing aspirin to placebo it really doesn't matter if the medical student or the chief of cardiology writes the order to administer the agent. This is not the case with surgical trials, where the skill and experience of the surgeon have profound effects on outcome. A study showing a benefit from surgery with a highly experienced group of surgeons will not be applicable if the outcomes of an individual surgeon fail to match those of surgeons in the study. Similarly, a study showing no surgical benefit may not be applicable if the study surgeons have outcomes significantly worse than a surgeon with exceptional skill and experience.

A final issue with surgical RCTs is their cost in time, effort and money. In order to have enough patients to properly power a study, large multicenter trials often are necessary. These are expensive, time consuming and labor intensive, making it difficult or impossible to repeat a trial, even if there are grave concerns about the validity of the study. Because RCTs often take many years to complete, their results may be meaningless if new technology has developed during the trial that could affect patient outcomes.

For all the reasons noted above, surgical RCTs are anything but a gold standard. They are unblinded studies, subject to observer bias, involving unrepresentative patients, treated by unrepresentative surgeons, who often do not have equipoise for the treatments offered. Furthermore, the fascination with null hypothesis testing often sets up a false dichotomy of treatment options when reality is much more multifaceted. This yields studies showing statistically significant differences that have no clinical significance and missing meaningful associations because we failed to reach a magic number of $p<0.05$. Science, especially clinical science, is messy. Trying to force messy data into the null hypothesis testing paradigm is almost always going to give us errant answers.

Bob

Robert E. Harbaugh, MD, FACS, FAHA
Hershey, Pennsylvania

Response of Professor AD Mendelow to comments by Dr RE Harbaugh

Dear All,

Bob's (Dr Robert Harbaugh) argument is easily refuted in some circumstances: If "sick" patients in observational studies are treated with surgery while "well" patients are treated non-surgically, the results will show that non-surgical treatment is better. But, all we would be showing is that "sick" patients do worse! One might then draw the wrong conclusion that surgery is ineffective. There are countless such examples. All the registers and databases in the world could be analysed with Bayesian or other methods and the same incorrect conclusions would be drawn.

Randomisation ensures that the proportion of "sick" to "well" patients is the same in the 2 groups. Blindness cannot be ensured in surgical trials but the outcome analysis can be done blindly by eliminating the investigator: telephone or postal questionnaires achieve this.

We should avoid throwing out the good that comes from clinical trials, just as we should appreciate where and when good observational data is all that we need: there has never been a randomised trial of smallpox inoculation but we have almost eliminated smallpox around the world. The same goes for smoking related diseases.

Let us therefore embrace all the good methods that can be used to assess our surgical practice and be well informed of the strengths and

weaknesses of each.

AD Mendelow FRCS PhD
Newcastle UK

Response of Dr Harbaugh to comments by Professor AD Mendelow

David,

I think we will have to agree to disagree. Registries need to be constructed with adequate attention to risk modifiers. If this is done, propensity analysis or regression analysis can look for associations between these factors and outcomes. In fact, I believe that registries are superior to RCTs in this respect. For instance, in surgical trials, one of the most important factors determining outcome will be the skill of the surgeon. This factor can be readily analyzed in a registry but is routinely ignored when applying the results of an RCT. If one can perform a carotid endarterectomy with a 2.5% perioperative morbidity and mortality the indications for this operation are different than if one performs the surgery with a 10% morbidity and mortality. Practice parameters based on RCTs assume that all surgeons have the same perioperative complication rates as the mean for the surgeons involved in the RCT.

In RCTs randomization is done to assure that confounding factors are equally distributed among the groups. In an adequately sized study this will work for those patients included in the study. However, as I noted in my previous examples, if equipoise does not exist, many confounding factors will be used to select patients for surgery outside of the trial. After this occurs, no randomization scheme can correct for this selection problem - but we apply the results of the RCT to all patients.

In regard to bias, using telephone or postal questionnaires does not eliminate bias because the patient is unblinded. This will always result in placebo effects. It is well documented that surgery has a significant placebo effect. In addition, if a patient believes that one treatment is more “advanced” or “modern” than another, the patient is likely to report superior outcomes for the newer procedure. Blindfolded persons taken for a ride in a Mercedes or Ford Taurus rate the ride about equally if they are unaware of the manufacturer. However, if the name of the vehicle is known the Mercedes ride is rated as superior. There is no reason to believe that the same principle does not apply to medical and surgical treatments. An unblinded study is a biased study and this bias may or may not be of clinical significance.

We do not want to throw the baby out with the bathwater but in the case of surgical RCTs there is a great deal of bathwater and I am still looking for the baby.

Bob Harbaugh

Robert E. Harbaugh, MD, FACS, FAHA
Hershey, Pennsylvania

Response of Mr G Solanki to comments by Dr Harbaugh

Dear Dr Harbaugh,

Your excellent presentation struck a chord in many of us. RCT are very expensive, take far too long and by the time they are finished a couple of newer techniques or devices have hit the market. You could of course go on forever doing such studies to ensure patients always knew which was the best technique or treatment choice, if indeed these trials did prove such a thing. Medical RCTs for drug efficacy & safety studies, are expensive in another way. For every day a drug spends in development, the pharmaceutical company loses an estimated $500,000 in sales revenue!

I would like to make some comments, There is some evidence in the literature to support your argument.

In 1946, the trial of streptomycin for the treatment of pulmonary tuberculosis was probably the first clinical trial that used randomisation for patient allocation. Sir Austin Bradford Hill (the statistician on the trial committee) is generally credited with introducing this innovative design. In 1964, the British

Medical Journal published a paper by Goligher, reporting the first randomised trial in surgery. This study compared three different operations for the elective treatment of duodenal ulcer (vagotomy with gastroenterostomy, vagotomy with antrectomy, and subtotal gastrectomy). Before this however, in 1961 Willey McKissock published in the Lancet a controlled trial of surgical and conservative treatment of intracerebral Haemorrhage in 180 patients (Lancet 1961, 2:221-226), probably the first controlled surgical trial in Neurosurgery.

Since then there appeared to have been an upsurge and the number of "surgical" trials increased rapidly to reach a peak in 1985 but dropped by 1995 at least in one British Surgical journal as depicted in figure 1(Pollock AV (1993) Surgical evaluation at the crossroads. Br J Surg 80: 964-966).

In 1994, Solomon at al. identified 202 RCT in surgery published in 1990 [Randomized controlled trials in surgery. Surgery 115: 707-712]. 76% of these trials compared medical therapies in surgical patients, only 18% compared surgical procedures and only 11 trials (6%) compared medical and a surgical treatment. Clearly RCTs in surgery are not as popular as they were in the first 2 decades after they were introduced.

I agree with Dr. Harbaugh that the patient's preference is amongst the greatest obstacles to such trials and this particularly applies to paediatric neurosurgery where most well-educated parents with ready access to the internet want the latest treatments provided for their kids and are prepared to travel long distances to receive it even when there is not a shred of evidence to support such a decision.

Equally it is self-evident to us neurosurgeons that the best surgery is the one we know how to do well, after years of perfecting our personal technique. In inexperienced hands, a better surgical technique may at best show no difference or at worst yield poorer results and greater complications. Thus the surgeon as part of the surgical treatment arm is already biased to his own surgical choice.
For the conduct of a proper RCT standardization of the surgical technique and the skills of the surgeons should be essential pre-requisites. However to achieve this one would have to re-train or train in a new technique for some time to overcome the problems associated with the surgical learning curve. This training or re-training brings its own problems. You may be unfortunate enough for the hospital or your peers to dissuade or even try to stop you from performing the new procedure for fear of complications or exposure to litigation. In the UK every new procedure must be registered with NICE and be meticulously followed up. If one passes this obstacle, and gets enough patients prepared to undergo surgery by one's "less" experienced hands, a stage is reached where you either dislike the technique and are biased against it or you get good at it and become its champion. Again equipoise is difficult to achieve.

In terms of blinding this is virtually impossible unless the size of the incision is similar when comparing two operative techniques. However when comparing non-surgical with surgical therapy this is not possible. The consent process itself will be transparent. There is also the placebo effect inherent in every operation. Previous trials showed a placebo effect of surgical procedures. Of course "Sham" surgery is no longer ethical.

However EBM (evidence based medicine) in its entirety is more than RCTs. We use Evidence Based Medicine in virtually every aspect of Neurosurgical practice. Patient assessment, establishing diagnosis, evaluation of interventions, determining prognosis and of course treatment efficacy. We review guidelines daily and report such data and information to patients. RCT evidence already exists for peripheral nerve surgery, antibiotic prophylaxis, epilepsy prophylaxis in Brain tumours, spinal cord injuries, odontoid fractures, cervical arthroplasty to anterior cervical discectomy and fusion, STICH, CRASH (Corticosteroid Randomisation After Significant Head Injury), and CRASH2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) is ongoing just to name a few.

I do agree that where double-blind RCT are not suitable, non-randomized comparative trials or consensus conferences can be attempted. Establishing a comparable control group and a

well-documented prospective cohort, including follow-up results for future comparisons is also acceptable.

One recent proposal that has attracted more rejection than support is that by Devereaux et al to consider ***expertise based randomised controlled trial***, which randomises participants to surgeons with expertise in intervention A or surgeons with expertise in intervention B, and the surgeons perform only the procedure they are expert in. The focus would be on established surgical interventions rather than new surgical procedures in which clinicians have not established expertise (BMJ 2005;330(7482):88). However, it can take years to define the level of expertise even if cases have been preferentially directed to the individual in question. Personal experience and expertise in a given procedure or area of interest has traditionally formed the basis of the outcomes reported in the literature. Raising this evidence from a class III to class I, raises some understandable concerns about suitability, using these data to make clinical decisions for and then have surgery performed by surgeons with lesser skills. Such trial results in general would not be applicable to a standard population of surgeons unless they were all experts and how can expertise be defined?
The introduction of Bayesian analysis of clinical data is certainly to be recommended. It should constitute the first step in the evaluation of the need for a RCT to help determine the chances of success and magnitude of change. Data from a pilot study, a systematic review of the literature would constitute advanced knowledge.

I think that RCTs are here to stay but do believe that your presentation and discussion has re-opened an important topic for discussion that should stimulate a more vigorous debate and improve the manner and quality of the RCTs of the future.

With kind regards

Guirish Solanki

Mr G Solank FRCSI FRCS(SN)
Birmingham

Response of Mr PL Grundy to comment of Mr G Solanki

I very much enjoyed this presentation on EBM and also the responses from Guirish Solanki. They both raise a number of very important issues and problems with so-called 'evidence based practice'.

I would like to point out that the RCT 'evidence' for antibiotic prophylaxis and anti-convulsant prophylaxis for patients undergoing neurosurgery is inadequate and incomplete and should perhaps not be used as example of EBM in neurosurgery

Happy New Year to all

PG

Paul L Grundy BM(Hons) MD FRCS(SN)
Southampton UK

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Invited Presentation

Malignant Gliomas Molecular Biology and Futures Perspectives

James T Rutka, MD PhD FRCSC FACS FAAP
(Toronto)

Questions to Dr Rutka from Mr G Solanki

Dear Prof. Rutka,

Congratulations on the excellent state-of-art review of the molecular biology and future perspectives in malignant gliomas. I found your review very helpful and it provided much food for thought.

1. Could you tell us your views on the immunotherapy in tumours particularly related to Reversal of Tumour induced Immuno-

suppression by TGF-B, transforming growth factors and Dendrite Cell vaccination for GBM?

2. In terms of differential expression of cellular division do you think that control proteins are going to be important in GBM?

3. Classification system for Gliomas:

The classification of gliomas is over 60 years old and while the Daumas-Dauport grading system has standardized characterization of astrocytic tumours it is becoming clear that the aetiology, behaviour, treatment outcome and prognosis of tumours vary in ways that histology can not always correctly determine or predict. Indeed using such a categorical system based solely on one dimension or parameter may eventually be shown to undermine the results in clinical trials and misguide us on treatment outcomes based on such classifications. Multiple researchers have shown that specimen review can reveal discrepancies in some 20-50% of the specimens (Giannini JNEP 2001; Fouladi, Cancer, 2003 (CCG 945); Coons Cancer 1997; Chastagner, PBC, 2007 (SFOP))

3. 1 How do you feel we should integrate the newer technologies you described to histological diagnosis?

Molecular-level characterization of tumours and development of diagnostic categories by CGH or CMA seems eminently reasonable and I am certain that before long we will have a device that will do this in real-time in our operating theatres. However this in itself will have a lesser impact unless we have developed a way to transfer this understanding to more user-friendly interfaces.

How do we put together the molecular signatures such as loss of 1p-19q with the up and down regulation of various signalling pathways? Are these changes tumour related or are they attempts by the body to protect essential cellular survival pathways? Targeting signalling mechanisms to destroy the tumour seems promising, yet alone it is probably not enough as some form of deactivation of tumour suppressors is probably ongoing in another dimension or part of the genetic imprint. Will damage to signalling pathways and DNA repair proteins such as MGMT cause future deregulation of Tumour suppressor genes and lead to other tumours or even more resistant tumours?

Our current diagnostic tools involve radiological imaging, particularly MRI with Contrast, MR Spectroscopy and Diffusion/Perfusion studies. There is now some evidence in the literature to suggest that in oligodendroglial tumours for example loss of 1p is associated with a frontal location of tumour, that loss 1p-19q is associated with indistinct GBM tumour borders on T1W with iso-signal and calcifications in T2W imaging (Jenkinson MD et al, Brain. 2006). A recent separate analysis of 96 GBM children has shown a difference in outcomes by sharpness of the tumour border, p=0.01 (Puget, Necker, 08 Verbal communication). A recent study using Dynamic MRI suggested that the maximum rate of uptake in dynamic MRI can be a prognostic measure for patients with malignant gliomas. While MRI Spectroscopy is regularly used in many centers for diagnostic purposes, their prognostic significance has not yet been determined in large studies, there is some data to suggest that pre-treatment MRI and three-dimensional 1H-MRS provide information that predicts outcome for patients with malignant gliomas.

3.2 Is there a role for a multi-dimensional classification system that identifies tumours based on internal correlation of all of these parameters?

The multiple dimensions could include classical radiological imaging, extended imaging techniques such as MR Spectroscopy, and genetic and molecular characterization, aetiological and phenotypic dimensions. The relationship between these dimensions may be just as important as the single dimensional findings, perhaps more so. Some findings make no sense in 2-dimensions but become very clear in 3 or more dimensions. Such a system would not only be diagnostic but may also specify the best therapy strategy and ultimately be predictive of outcome.

3.3 Could Operational Multiple-Input Neural Networks (that include inputs from multiple dimensions) be a way forward?

The software technology for Molecular CGH / cDNA analysis requires some fine-tuning if we are to find which tumours will respond to which therapies. Inclusion of inputs from other investigative and therapeutic modalities particularly where disparate and sparse data in many dimensions exists requires non-conventional methods for prediction and factor analysis.

Apologies for the long question.

Kind regards

Guirish Solanki FRCSI FRCS(SN)
Birmingham, UK

Response of Dr Rutka to questions from Mr Solanki

Dear Mr Solanki,

I know the session is now closed, but here are the answers to your

questions. Thanks for asking them. I was busy on call over the holidays,

and could not participate as I had hoped.

Sincerely,

Jim Rutka

1. Could you tell us your views on the immuno-therapy in tumours particularly related to Reversal of Tumour induced Immuno-suppression by TGF-B, transforming growth factors and Dendrite Cell vaccination for GBM?

Immunotherapy for brain tumors, especially gliomas, holds considerable promise. A trial at Duke University using an immunotherapy vaccine is gaining a lot of attention. Early results look promising. Over coming tumor suppression by TGF-B will always be a challenge, and this issue has not been completely solved yet.

2. In terms of differential expression of cellular division do you think that control proteins are going to be important in GBM?

There is no question that hierarchies of control proteins will be involved in GBM. Our job will be to determine what these hierarchies are, and to develop targeted strategies against them.

3. *Classification system for Gliomas:*

The classification of gliomas is over 60 years old and while the Daumas-Dauport grading system has standardized characterization of astrocytic tumours it is becoming clear that the aetiology, behaviour, treatment outcome and prognosis of tumours vary in ways that histology can not always correctly determine or predict. Indeed using such a categorical system based solely on one dimension or parameter may eventually be shown to undermine the results in clinical trials and misguide us on treatment outcomes based on such classifications. Multiple researchers have shown that specimen review can reveal discrepancies in some 20-50% of the specimens (Giannini JNEP 2001; Fouladi, Cancer, 2003 (CCG 945); Coons Cancer 1997; Chastagner, PBC, 2007 (SFOP))

It used to be said that the final arbitrator of the pathology was thepathologist. This is no longer true, for the reasons you stated. Very soon, the diagnosis of human brain tumors will rest in the hands of the molecular biologists, and not the neuropathologists.

3. 1 How do you feel we should integrate the newer technologies you described to histological diagnosis? Molecular-level characterization of tumours and development of diagnostic categories by CGH or CMA seems eminently reasonable and I am certain that before long we will have a device that will do this in real-time in our operating theatres. However this in itself will have a lesser impact unless we have developed a way to transfer this understanding to more user-friendly interfaces.

How do we put together the molecular signatures such as loss of 1p-19q with the up and down regula -tion of various signalling pathways? Are these changes tumour related or are they attempts by the body to protect essential cellular survival pathways? Targeting signalling mechanisms to destroy the tumour seems promising, yet alone it is probably not enough as some form of deactivation of tumour suppressors is probably ongoing in another dimension or part of the genetic imprint. Will damage to signalling pathways and DNA repair proteins such as MGMT cause future deregulation of Tumour suppressor genes and lead to other tumours or even more resistant tumours?

Our current diagnostic tools involve radiological imaging, particularly MRI with Contrast, MR Spectroscopy and Diffusion/Perfusion studies. There is now some evidence in the literature to suggest that in oligodendroglial tumours for example loss of 1p is associated with a frontal location of tumour, that loss 1p-19q is associated with indistinct GBM tumour borders on T1W with iso-signal and calcifications in T2W imaging (Jenkinson MD et al, Brain. 2006). A recent separate analysis of 96 GBM children has shown a difference in outcomes by sharpness of the tumour border, p=0.01 (Puget, Necker, 08 Verbal communication). A recent study using Dynamic MRI suggested that the maximum rate of uptake in dynamic MRI can be a prognostic measure for patients with malignant gliomas. While MRI Spectroscopy is regularly used in many centers for diagnostic purposes, their prognostic significance has not yet been determined in large studies, there is some data to suggest that pre-treatment MRI and three-dimensional 1H-MRS provide information that predicts outcome for patients with malignant gliomas.

I predict in the future we will not need to biopsy tumors to establish their diagnoses. Rather, the latest imaging technologies will be sufficient to make the diagnosis with accuracy. However, we may need biopsies so that the sophisticated molecular maps can be created as fingerprints for each tumor type for each patient.

3.2 Is there a role for a multi-dimensional classification system that identifies tumours based on internal correlation of all of these parameters?

The multiple dimensions could include classical radiological imaging, extended imaging techniques such as MR Spectroscopy, and genetic and molecular characterization, aetiological and phenotypic dimensions. The relationship between these dimensions may be just as important as the single dimensional findings, perhaps more so. Some findings make no sense in 2-dimensions but become very clear in 3 or more dimensions. Such a system would not only be diagnostic but may also specify the best therapy strategy and ultimately be predictive of outcome.

No question, this is the wave of the future.

3.3 Could Operational Multiple-Input Neural Networks (that include inputs from multiple dimensions) be a way forward? The software technology for Molecular CGH / cDNA analysis requires some fine-tuning if we are to find which tumours will respond to which therapies. Inclusion of inputs from other investigative and therapeutic modalities particularly where disparate and sparse data in many dimensions exists requires non-conventional methods for prediction and factor analysis.

Not so sure about this one!

James T. Rutka, MD, PhD, FRCSC, FACS, FAAP
Toronto

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Invited Presentation

Day-Case Neurosurgery for Brain Tumours

Paul L Grundy, BM(Hons) MD FRCS(SN) (UK)

Question from Dr RA Fink to Mr PL Grundy

Did the authors query the patients as to whether the abbreviated hospital stay was appreciated or not? Some patients, in my experience, prefer to spend a day or two in the hospital for the "creature comforts" thereof.

Best,

Robert A. Fink MD
Berkeley

Response of Mr PL Grundy to Dr RA Fink

At the time of the consultation we did not ask patients about their preference for overnight stay but did ask them before they were discharged home - you will see from the data that a very small number were then admitted post-op out of preference.

However, I am afraid that a busy regional neurosurgical ward in the NHS in UK does not offer patients many 'creature comforts", hence the reason most are very delighted to be able to go home I guess! We find they prefer this on the whole.

We are now doing retrospective satisfaction survey of all our awake cases and will see if there is any difference between those who are day-cases and those who stay overnight.

Interestingly I have re-operated on 3 craniotomy cases now who were day-cases and they all specifically asked if they could be day-case for re-operation.

PG

Paul L Grundy BM(Hons) MD FRCS(SN)
Southampton

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Invited Presentation

Management and Treatment of Cerebral Vasospasm

Bartosz T Grobelny BA, Reshma Narula BA, Brad E Zacharia MD, E Sander Connolly Jr MD (New York)

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Invited Presentation

Minimally Invasive Lumbar Interbody Fusion

John Ratliff, MD and Gabriel Tender, MD
(Philadelphia and New Orleans)

Question from Mr G Solanki to Dr J Ratliff

Dear Dr Ratliff,

Congratulations on such a wonderful job in simply but clearly presenting the data and the excellent video which was indeed very useful. This is a newer technique and you have highlighted that in good and properly trained hands the MIS and specifically TLIF seems to be just as good as open procedures with no significantly higher short-term penalties for the patient.

1. I would be obliged if you could propound a little more on when you would consider using an XLIF or ALIF instead of a PLIF or a TLIF in this group of degenerative disc and mild grade1spondylolisthetic patients. Is it weight and co-morbidity related or do you have a rule of thumb? What is your system to decide that a "fusion" is now due?

2. How do you find these procedures compare to the less "internally fixed" ADR (artificial disc replacement) when it is a single-level disease? Particularly preservation of mobility may have a role to play in younger patients in terms of saving the next segment.

3. Are there any long-term evaluations on the effect of unilateral facet destruction in MIS TLIF? What is the longest follow-up reported?

4. Finally will the addition of rhBMP-2 with ACS vector within a cage in PLIF or TLIF obviate the need for instrumented pedicle screw fixation as well? Grateful for your opinion.

Kind regards

Guirish

Mr G Solank FRCSI FRCS(SN)
Birmingham, UK

Response of Dr Ratliff to questions of Mr G Solanki

Thank you for your kind and thoughtful questions. I will respond to each in turn.

First, your initial comments are exactly correct. MIS approaches to the spine are simply another approach to the same goals as classic open surgical techniques. They do not expand the population of patients being treated, nor are they a replacement for proper pre-operative evaluation. In MIS surgery, as in all other aspects of surgical treatment for the spine, the best predictor of patient outcome is pre-operative patient selection.

1. The XLIF is a promising new approach using a lateral approach to the spine. Depending upon patient anatomy, it is often only feasible in the mid-lumbar spine. Due to the iliac crest, it is often difficult or impossible to reach L4-5 or L5-S1 with an XLIF approach. For our multiple level adult degenerative scoliosis patients with a coronal curve centered in the mid-lumbar region, the XLIF is a fantastic means of achieving deformity correction and providing a substrate for fusion.

I still default to the classic open ALIF, usually augmented with percutaneous pedicle screws, for my patients with well preserved disc height where I am concerned over being able to position an adequately sized interbody graft through a posterior approach. Also, in my hands I can achieve more fulfilling correction of a isthmic spondylolisthesis in younger patients with an anterior approach, although this is certainly a controversial point.

How do I decide when a fusion is necessary? That is a topic that could occupy an entire conference on its own. In my present practice, I find myself using arthrodesis procedures in adult deformity, recurrent disc herniations, and, much more rarely, degenerative disease with intractable axial pain.

2. My concern with lumbar ADRs remains revision strategies. I find that I am much more selective with use of the Charite and other ADR devices. I believe they do have a role in younger, more active patients, but in our experience at Jefferson the initial interest in these devices, both from surgeons and the lay public, has waned in favor of more classic reconstructive approaches.

3. Presumably the effects of the unilateral facetectomy is countered by the stabilization procedure. The majority of published reports offer short-term follow-up, as reviewed in my presentation. A recent review by Dhall et al. offered 24 month follow-up in MIS TLIF patients, with good clinical results (Journal of Neurosurgery: Spine. Vol 9: 560-565, 2008). While the early reduction in pain and peri-operative blood loss with minimally invasive surgeries should be evident with short term follow-up, some proponents of the techniques note that the limited damage to lumbar paraspinal musculature may have longer beneficial effects. Longer term follow-up of these patients is necessary.

4. I would offer two responses with regard to BMP: Biologics are not a replacement for operative technique. Proper end-plate preparation and proper preparation of the fusion bed are necessary. Number 2, I do not believe biologics replace appropriate internal fixation. In the published Infuse data, looking at ALIF procedures, fusion maturity was not reached until 1 to 2 years after the index procedure. With a potentially destabilizing procedure (facetectomy, discectomy, likely combined with a decompressive laminectomy), I still believe internal fixation is necessary.

Thank you again for your consideration of my presentation and of Dr. Tender's video.

John Ratliff MD
Phildelphia

Question of Dr J Loeser to Dr J Ratliff

For Ratliff Minimally Invasive Surgery: Although there is data presented on fusion rate and complications, nothing is said about outcomes, such as post-operative pain level, drug utilization, functional status, return to work. The goal of surgery is more than to perform a technically successful operation in a timely fashion; a person

is more than a collection of parts.

John D Loeser MD
Seattle

Response of Dr J Ratliff to question of Dr J Loeser

Excellent points. The purpose of my presentation was to focus upon technical aspects of the procedure, as an introduction to MIS approaches for an international audience. Hence, my brief presentation necessarily glossed over outcomes data.

I would refer interested readers to the Dhall et al. article (J Neurosurg Spine 9: 560-565) mentioned in my last email, or perhaps to Fessler's earlier report of his clinical outcomes in comparison to open PLIFs (J Neurosurg Spine 3: 98-105). Both offer clinical data showing either trends or clear superiority in MIS approachs with regard to blood loss, length of stay, and post-operative narcotic use.

Both, however, are retrospective reviews with the obvious possibilities for investigator bias. No prospective studies, to my knowledge, have been reported comparing MIS and open interbody techniques.

I would also proffer, in contradistinction to your closing remarks, the goal of surgery actually is to perform technically successful operations. The harder task of being a surgeon is realizing where and when those tools should be utilized.

John Ratliff MD
Philadelphia

♠

Invited Presentation

Current state of Neurosurgery for Parkinson's Disease

Konstantin V Slavin MD (Chicago)

Question from Mr G Narenthiran to Dr K Slavin

Dear Konstantin,

I enjoyed studying your excellent comprehensive presentation on the current state of surgery for the management of Parkinson's disease. A number of questions for you:

1) When you get consent from your patients for DBS for PD, what do you say is the chance of benefit and degree of benefit patient can expect in practical terms in their life following the surgery? How long is the benefit going to last? Patients' expectations can be high; has there been any study on 'Patient satisfaction'?

2) One of the slides ('Recent randomized STN DBS Data') states that the death in patients who had underwent surgery was 3. In those treated medically only 1 patient died. How can surgery be better than medical treatment if there are more deaths associated with surgery (even if other complications are more in medically treated patients)? This goes back to how you measure outcome and make value judgement on the outcome.

Thank you and look forward to hearing from you.

Yours sincerely,

Naren

G Narenthiran BSc(MedSci)(Hons) MB ChB MRCSE
Southampton

Response of Dr K Slavin to question of Mr G Narenthiran

Dear Naren,

Thank you for your thoughtful review! (and for

putting this all together!!!)

To answer your questions:

1. I routinely tell all patients that the degree of improvement with surgery is really unpredictable. So far, all patients that I operated on have improved – but some improved to complete independence with no medications, while others had only minimal symptomatic changes. Same goes for the duration of improvement – it varies dramatically from person to person, but in most cases this improvement stays for a long time. In general, I am not a big supporter of quoting percentages to the patients since each of them may fall into a very small group of "minimal responders" or have a complication from surgery – an in this case the fact that "90% of patients would improve significantly" would sound even more depressing… The decision for surgery is a very individual one – and I really try to get these patients come to terms with all risks, surgical discomforts, and follow up hassles (adjustment of stimulation settings, need in battery changes, etc.) before they consent for surgery. I also frequently insist on them talking to those who already had surgery so this new experience (frame, awake operation, staged implantation) does not become an unpleasant surprise (patients frequently forget or ignore a lot of information from their physicians – but seem more receptive to their peers). The patient satisfaction has been studied and presented at conferences (I am not sure if it ever been formally published) – and the patients are generally satisfied with surgery and would definitely have it done again if given a choice.

2. You are absolutely right – the risks of surgery are not negligent, by any means. The truly surgical death in this study was in patient with ICH – the other three were possibly unrelated to the treatment choice (suicide, psychosis, pneumonia) as the natural history of advanced PD has its own mortality. This constitutes 1.5% surgical mortality – and I always bring it up in my discussion with patients. In addition to the risk of death, stroke or hemorrhage (all of which seem to increase with age, degree of brain atrophy, presence of previous strokes, anticoagulation, etc.) I quote a general risk of surgical complications (infections, erosions, disconnections, malfunctions, etc.) at 20-30%, intentionally increasing it for those in doubt – and then let the patient and family decide if they still want to proceed with operation.

Happy New Year!

K.

Konstantin Slavin MD
Chicago

Question of Dr A Fillipidis to Dr K Slavin

Dear Professor Slavin,

Congratulations for your thorough presentation!

I would like to ask you about the existence of absolute of relative contraindications concerning the procedure of subthalamic nucleus DBS. Are there any concerns in your practice that would affect your decision for selecting a patient for STN DBS ?

I would like to thank you in advance,

Best regards,

Aristotelis Filippidis MD
Larissa, Greece

Response of Dr K Slavin to question of Dr A Filippidis

To Dr. Filippidis:

There are multiple contraindications for STN DBS procedure: and some are more obvious than others.

In general, STN DBS is recommended for advanced cases of levodopa-responsive PD who did not have previous destructive surgery – this, I believe, is a formal wording from FDA approval

for the procedure.

* We do not routinely recommend this surgery for those with dementia or severe brain atrophy.

* Use in very early or very advanced (terminal) stages of PD has not been justified so far.

* Presence of active infection or uncorrectable coagulopathy would also serve as a contraindication.

* Presence of pacemakers and defibrillators would be considered a contraindication by many (mainly due to inability to get MRI for targeting, but also due to concerns of electrical interference, particularly with on-demand defibrillators).

* Many places, ourselves included, would not consider STN DBS for Parkinson Plus syndromes (progressive supranuclear palsy, multiple system atrophy, Lewy bode dementia, etc.)

* Inability to provide a follow up (due to geographic limitations, for example), or lack of appropriate social support (family, etc.) would be relative contraindications as well.

* Two most frequent occasions where we would consider going "off label" would be those who do not respond to levodopa in predictable fashion and those who had previous Thalamotomy or Pallidotomy – although I do not have much data to support this.

* There are many other exceptions to the standard inclusion/exclusion protocol, but these are the main ones.

* Yet another big concern is the lack of realistic expectations (from patients, families, referring physicians)…

Best regards,

K.

Konstantin Slavin MD
Chicago

♠

Invited presentation

Management of Spasticity in Children

George Jallo, MD (Baltimore]

Question of Mr G Solanki to Dr G Jallo

Dear George,

Congratulations on the comprehensive cover of the topic of managing spasticity.

I would like to ask a few questions;

Mr Solanki: Test dose for ITB: How do you perform your test doses? Do you offer your paediatric patients a single LP delivered daily, sequentially increasing the dose of IT Baclofen on different days or insert a lumbar drain and deliver the sequential doses that way? In either case, how long do you keep the children in? In Europe, some units prefer to use an internalized system with a reservoir (implanted at the final site for the pump) to allow a blinded placebo-controlled sequential dose evaluation. The patient would stay approximately 5 to 7 days for the testing and this provides parents with a good way to evaluate the response not just in muscle tone and spasm frequency but as you rightly pointed out in the presentation the unwanted effects in reducing "good tone" with some loss of posture maintenance and strength. It may also allow for evaluation of sometimes borderline or masked oropharyngeal dysmotility which can cause silent or overt aspirations and or require PEG feeding post-implantation. Similarly head tone and head holding can get affected and such an extended period of evaluation may be considered worthwhile. I am grateful for your comments.

Dr Jallo: I have found that the single injection LP work for 95% of the children if chosen properly. If they do not respond then I implant the catheter and reservoir for continuous infusion. And in these cases I reach about 99% implantation rate. I really do the screening prior to surgery.

Mr Solanki: Pocket implant: Prior to surgery we usually identify the implant site. In children with very high catabolic rates and little or no subcutaneous tissue. In some of these difficult cases we now create a deep pouch for implant placing the pump in a subfascial position within the muscular layer. We recently found in a case of advanced lumbar hyperlordosis with severe

scoliosis, that the abdominal route was no longer workable with recurrent extrusions of the pump. We landed up moving the pump to the contra-lateral side and finally in a submuscular pectoral position after using tissue expanders. Have you had any such problems and how did you solve them?

Dr Jallo: All get a subfascial implantation of the pump as it prevents exclusion. The only subcutaneous implants are in the adults

Mr Solanki: Catheter tip position: It is generally accepted that for spastic diplegia with abdominal muscle spasm the tip should be somewhere around T10 level, and for spastic tetraparesis, the tip should be brought up between the upper thoracic to mid-cervical levels. More recently there has been a suggestion that the catheter tip position does not correlate well with clinical response. I would be grateful for your opinion.

Dr Jallo: I try to get the catheters around T9 for the diplegia and C5 to T2 for the quad spasticity. It does correlate with the level of placement

Mr Solanki: Precautions & Recent medical alerts: MRI: Magnetic Resonance Imaging (MRI) will temporarily stop the pump motor and suspend drug infusion for the duration of MRI exposure. Although the pump should resume normal operation after MRI exposure it is sensible that before and following completion of an MRI scan, the pump parameters are re-confirmed and re-programmed. Also for MR scanners greater than 2 Tesla, the safety and performance of the programmable pumps are not known and these scanners are therefore contra-indicated. We are currently discussing national guidance for MRI & ITB pumps given the above. I would be very grateful for your comments.

Dr Jallo: I always confirm after the MRI the pump setting.

Guirish

Mr G Solank FRCSI FRCS(SN)
Birmingham, UK

Dr G Jallo MD
Baltimore, Maryland

Question from Dr Filippidis to Dr G Jallo

Dear Prof. Jallo

I'd like to express my congratulations for your presentation and wish to everyone happy holidays from Greece!

My questions:

Dr Filippidis: Are there any age related limitations in applying Intrathecal Baclofen pump devices concerning children ?

Dr Jallo: No just a weight limit. My cutoff is 30-35 pounds

Dr Filippidis: What is your smallest age experience of applying this treatment modality and what is the mean pediatric age of treatment?

Dr Jallo: 18 months is the youngest child mean age is 5or 6

Dr Filippidis: Are there complications specifically related to pediatric populations?

Dr Jallo: Yes, it is the pump related and wound healing issues as it is a large pump in relatively thin children.

Best regards,

Aristotelis FIlippidis MD
Larissa, Greece

Dr G Jallo MD
Baltimore, Maryland

♠

Invited presentation

Transarterial vs Direct Percutaneous Embolization in the pre-operative treatment of renal cell spinal metastasis

Clara R Epstein, Bourekas EC, Gabriel JP, Ammirati M [Ohio]

♠

Original work

Twenty-seven years Experience in the Treatment of Moyamoya Disease (1982-2007)

Quintana Leonidas MD, Massaro Paolo MD, Gonzalez Francisco MD, Yokota Patricio MD, Segovia Miguel (Chile)

Aim

Moyamoya is a chronic cerebrovascular occlusive disease, with progressive stenosis of the intracranial carotid arteries and main branches, with development of a mesh of small vessels at the basal ganglia, to improve the collateral circulation, the moyamoya vessels. This disease is most frequently reported in asian countries, as Japan, Korea and China

Method

From 1982 to 2007 we treated 15 cases with Moyamoya Disease :7 males and 8 females, 6 - 51 years old. We observed 2 groups :

Ischemic presentation: 7 cases

Hemorrhagic presentation: 8 cases

All cases were studied with 4 vessels angiography and CT, and 5 cases with MRI.

The first 10 cases(1982-2000), were treated with Encephalo-dural-arterial-sinangiosis.The last 5 cases (2001-2007) were treated with Encephalo-dural-galeo-arterial-sinangiosis, plus burr-holes.

Results

In 6 cases, the clinico-morphological presentation were atypical compared with those described in oriental countries.

In 4 cases with hemorrhage, the moyamoya vessels were unilateral, 1 case with ischemia, moyamoya were unilateral, 1 hemorrhagic case presented with early bilateral cervical internal carotid occlusion.

Functional outcome evaluated at 12 months after the operation:

1. Returned to normal life: 4 cases

2. Active with mild limitations: 5 cases

3. Active with severe limitations: 5 cases

4. Vegetative: 1 case.

Conclusion

We concluded that in our experience the pattern of the arteritis is somewhat different from the cases reported in oriental countries, but the common fact is the presence of moyamoya vessels; the other conclusion is the functional prognosis depend of the initial cerebral damage, and those early operated cases had a better prognosis.

Key words
Moyamoya disease, cerebral arteritis, revascularization, chronic ischemia

Competing interests:

None

Question from Dr Fady Charbel to Professor L Quintana

I congratulate Prof. Quintana and his colleagues for a very nice review of the topic of Moya Moya and for presenting their 27 years of experience with the surgical management of this disease in Chile. It is interesting to note that their series include an almost equal distribution of pediatric (mostly ischemic) and adult (mostly hemorrhagic) patients. They achieved overall excellent revascularization (14/15 patients) with indirect bypass.

My question is this: I note that the surgery evolved over the years from the classical EDAS to the addition of wider flap and galeal/periosteal synangiosis. Would the authors care to explain the reason for their change in surgical strategy and if they are now considering adding direct revascularization (with STA-MCA) bypass to their approach.

Best regards,

Fady T Charbel MD FACS
Chicago

Response of Professor L Quintana to Dr F Charbel

Dr.Fady Charbel.

Thanks for your question.

Since 1982, when we made the first EDAS in Chile, to the present days, in the pattern of control angiography at 6 to 12 months post-surgery, progressively we noted that when the extension of the galeal tissue-STA artery was increased, we expanded the contact surface of this tissue with the ischemic cortex, and the sinangiosis was more effective, with more vessels of neovascularization over the ischemic brain tissue.

What we have added is the practice of Burr Holes (Endo M, Kawano N, Misayaka Y, Yada K: Cranial burr hole for revascularization in moyamoya disease. J Neurosurg 71:180-185,1989), and put periostium over the brain surface at this points.

That is a very simple technique, and complements the indirect revascularization in good shape.

The direct STA-MCA bypass we have not done routinely in cases of chronic ischemia, because usually the recipient artery is very thin, and the risk of failure in the direct by-pass is present.

Leonidas

Leonidas Quintana MD
Valparaiso, Chile

♠

Original work

The Effects of the Results of the STICH Trial on the Management of Spontaneous Supratentorial Intracerebral Haemorrhage in Newcastle-upon-Tyne, England

Matthew A Kirkman, Wattana Mahattanakul FRCS(SN), Barbara A Gregson PhD, A David Mendelow PhD FRCS (UK)

Department of Neurosurgery, Regional Neurosciences Centre, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE, United Kingdom.

Aim:

The role of surgery for spontaneous supratentorial intracerebral haemorrhage (ICH) remains controversial. Recently, the Surgical Trial in IntraCerebral Haemorrhage (STICH) showed no overall benefit from early surgery when compared with initial conservative treatment. Our aim was to evaluate the impact of the STICH trial results on management of ICH in the Newcastle upon Tyne Hospitals.

Method:

The STICH results were released to the trial's coordinating centre, the Neurosurgery Department at Newcastle General Hospital, in November 2003. Using ICD-10 data, we analysed ICH admissions before (2002) and after (2004, 2006, 2007) this. We assessed numbers of Neurosurgery and Stroke Unit admissions, numbers of clot evacuation procedures, and 30-day mortality rate (Neurosurgery versus Stroke Unit admissions). Subarachnoid haemorrhage (SAH) admissions data were also collected to corroborate our findings.

Results:

There were 478 spontaneous supratentorial ICH admissions in total; 156 in 2002, 120 in 2004, 106 in 2006 and 96 in 2007. SAH admissions remained remarkably constant over this period. Neurosurgery admissions for ICH decreased significantly across the four time periods, from 71% of total ICH admissions (n=156) in 2002 to 55% (n=96) in 2007, and Stroke Unit admissions increased significantly from 8% (n=156) in 2002 to 30% (n=96) in 2007 (χ^2=20.968, p<0.001, df=3). Clot evacuation procedures also decreased significantly from 32% (n=111) of Neurosurgery admissions in 2002 to 17% (n=53) in 2007 (χ^2=11.919, p=0.008, df=3). 30-day mortality increased in Neurosurgery, from 14% of Neurosurgery admissions (n=111) in 2002 to 26% (n=53) in 2007, and decreased in the Stroke Unit, from 42 % of Stroke Unit admissions (n=12) in 2002 to 17% (n=29) in 2007.

Conclusion:

The STICH results have significantly impacted ICH management in Newcastle, with a trend towards fewer Neurosurgery admissions and clot evacuations, and increased Stroke Unit admissions. Randomisation continues in STICH II for patients with superficial lobar ICH.

Competing interests:

ADM is a director of the Newcastle Neurosurgery Foundation and has received honoraria for serving on the advisory committees of Codman and NovoNordisk. The other authors report no conflicts of interest.

Questions of Dr F Charbel to Dr MA Kirkman

I congratulate Dr. Kirkman and colleagues from Newcastle for an informative presentation which seems to suggest that the public dissemination of the results of a clinical trial can influence the practice patterns of communities at large.

My question is this: Do you believe based on your findings concerning the drop in referrals to neurosurgical care,that an unjustified nihilism concerning the care of patients with ICH is starting to prevail? In other words, is could of the conclusions of your analysis be that, patients with ICH which may be candidates for surgical evacuation, are now kept at smaller hospital and possibly suffer worse outcomes?

Congratulations Naren for this work.

Best regards,

Fady.

Fady T. Charbel MD FACS
Chicago

Question of Professor L Quintana to Mr MA Kirkman

In relation with the interesting work "The effect of the results of the STICH Trial on the Management of Spontaneous Intracerebral Haemorrhage supratentorial in Newcastle upon Tyne, England", of Dr.Kirkman et al.; this study has shown that the total number of admissions to the Newcastle upon Tyne Hospitals NHS Foundation Trust have declined gradually from 2002 ! to 2007.(slide8)

I think this speaks in favor of better control of risk factors to suffer an ICH, but that isn´t an impact on how STICH management could affect this condition.

This initial condition could influence, in this study, the subsequent statistical analysis as a decrease in clot evacuation procedures for ICH, that decreased significantly from 32% (n = 111) of Neurosurgery admissions in 2002 to 17% (n = 53) in 2007 ($\chi 2 = 11,919$, $p = 0.008$, $df = 3$).

Leonidas Quintana MD
Valparaiso

Response of Mr MA Kirkman to Questions of Dr Charbel and Professor Quinatana

Dear Dr. Charbel and Professor Quintana,

Many thanks to both of you for your feedback and questions. Both your questions address similar points so it is perhaps best to answer them together.

Our main justification for the drop in ICH admissions is that the smaller hospitals lacking neurosurgical care facilities are referring less patients to Newcastle on the basis that the STICH trial suggested that a majority of cases would not benefit from neurosurgical intervention as opposed to conservative management through a stroke unit. There are of course exceptions where neurosurgical intervention would be indicated (space-occupying ICH, post-operatively and when the ICH has resulted from trauma, for example), and those with small haematomas are usually best managed conservatively.

Certainly, deciding who would benefit from surgery and who would not can be a difficult decision for the peripheral hospitals to make. However, given the current constraints on neurosurgical beds and financing in the National Health Service in the UK, there is always going to be an economic factor in the decision making process of whether to refer to a tertiary centre or not. As a result, there are inevitably going to be some who will suffer adverse outcomes in smaller hospitals as they lack the neurosurgical intervention that they require.

Perhaps an improvement to this study would have been to look at referral patterns for the patients included in our study, and to see how many patients were referrals from smaller hospitals, and how many patients were direct admissions from areas close to the main Newcastle hospitals. Including prognostic data (GCS at admission, age, volume of haematoma, etc.) would allow us to compare thresholds for neurosurgical intervention in the smaller hospitals vs. Newcastle hospitals and outcome data would indicate how these patients in the smaller hospitals fare compared to those admitted to Newcastle.

Personally I do not feel that the drop in ICH admissions reflects a change in ICH incidence. We collected admissions data for subarachnoid haemorrhage to act as a baseline comparison, and SAH admissions remained remarkably constant over the four years of our study - there were 192 SAH admissions in 2002 and 195 in 2007. This helps corroborate the idea that the drop in ICH admissions is due to a genuine change in referral patterns as opposed to a reduced incidence in haemorrhagic brain insults. I also suspect the markedness of the drop in ICH admissions (a drop of over a third in five years; 156 in 2002 to 96 in 2007) goes against an improvement in risk factors being the cause of the ICH admissions drop. Of course the definite answer to whether there has been a reduction in the incidence of ICH due to improved control of risk factors etc. would be a large scale epidemiological study.

I hope I have answered your questions adequately.

Best wishes and thank you again for your interest,

Matthew Kirkman

Newcastle

Comment by Professor Quintana

Thank you very much Dr Kirkman for your very complete explanation.

But, according with recent data, the growing of the haematoma volume, during the first hour, until the third hour of evolution, is a very important prognosis factor, for the posterior functional evolution of the patients.

I don´t know the programme related with prevention of vascular diseases in the Newcastle region, but in my region, Valparaiso (V) region of Chile, we teach to the general medical doctors of small hospital (V region has about 1.600.000 habitants), that they must send the patients to our base hospital Carlos Van Buren Hospital, as soon as possible, were they receive a very simple medical management , that is Tranexamic Acid 2gr at admission, after the CT Scan showing the hematoma, and haemodynamic control, mainly, not permit to have sustained Systolic Blood Pressure over 160 mmHg. (Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, Heeley E, Skulina C, Parsons MW, Kim JS, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Heritier S, Morgenstern LB, Chalmers J; INTERACT Investigators. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008 May;7(5):391-9).

After that,in our base hospital, according with the topography, and the evolution of the patient, clinically and with CT Scan controls, the neurosurgeon decide if they remain in medical treatment in the ICU , or go to surgery.

So my question is to know your opinion about the management in the small hospitals, of the very important prognosis factor that is the growing of the haematoma volume during the first hours of evolution?

With my best regards

Leonidas M Quintana MD
Valparaiso, Chile

♠

Original Work

Awake Craniotomy for Brain Tumours: a Prospective Study of a Simple Technique

Paul L Grundy BM(Hons) MD FRCS(SN), Crispin WeidmannFRC, Victoria Beasley (UK)

Comments of Dr Andrew Russell

My congratulations on the 4th International Neurosurgery Conference - a great advance in the era of limited time & travel resources!

Two comments:

1. Paul Grundy's presentation on 'outpatient awake biopsy/craniotomy' nicely outlines what is possible presently in our financially-constrained medical situation. Might I add that NOT shaving or clipping the hair before cranial procedures can be a part of efficient surgery. I have not clipped or shaved for a decade now, and not only see infections extremely rarely - but also virtually no drainage from the incision (usually linear if possible) so that a dressing is superfluous.

Best wishes, Russell

Russell J Andrews MD
Moffett Field, California

♠

Original Work

Sugar Cane Biopolymer Membrane as Dura Mater Substitute in Wistar Rats

Frederico de Melo Tavares de Lima MD PhD, Joacil Carlos da Silva Junior MD MSc, Roberto Jose Vieira de Mello MD PhD, Jose Lamartine de Andrade Aguiar MD PhD (Brazil)

Aim: To determine the utilization of the sugar cane biopolymer membrane patch as a dural substitute in rats.

Material and Methods: Forty adults males Wistar rats weighing 300-440g were randomly divided into two groups: a control and an experimental. Bilateral frontoparietal craniectomy was performed, and a dural defect was created. The arachnoid underlying defect was disrupted with a narrow hook. In the control animals, the defect was repaired with a disc of ePTFE. The experimental group received a membrane of sugar cane biopolymer over the cerebral cortex. No sutures in the dural patch were used in all cases. At the end of the procedure, the scalp was closed primarily in two layers. The rats were killed at 120 days. The heads were fixed by an intra-arterial injection, followed by immersion in 10% formalin solution. After seven days of fixation, the specimens were embedded in paraffin, and the dural substitute and subjacent brain were collected en bloc. Histological sections of the biopsies were stained with hematoxilyn/eosin and evaluation was performed comparing healing and inflammatory reaction.

Results: All the animals survived to the period of 120 days to clinical observation. There were no cases of infection, cerebrospinal fluid fistulae, delayed hemorrhages, behavior disturbances, seizures and palsies. The histopathological changes of leptomeninges were semi-quantitatively scored according the inflammatory responses or foreign body reaction in the outer and inner surfaces of the membrane, the host capacity in contention the implants, and the propensity in assimilate the prosthesis. The histological findings didn't demonstrate statistical difference between groups concerning the parameters analyzed except that the biopolymer has been slowly absorbed ($p<0.001$).

Conclusions: The sugar cane biopolymer membrane can be used as dural substitute in rats and it evolves to be absorbed by the hostess.

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Case Presentation

Primary dural Lymphoma Mimicking a Subdural Hematoma: a Case Report

Gocmen Selcuk MD (Turkey)

We describe a case of a woman, in whom a MALT (mucosa-associated lymphoid tissue)-type marginal zone B-cell lymphoma presumed to be a SDH was later identified. A review of the literature on primary dural lymphoma is presented.

Materials / Method

A 45-year-old woman who had generalized tonic clonic seizures and speech disturbances for six months was referred to neurosurgery department. The radiological findings suggested that it could be a subdural hematoma (SDH). Although the initial diagnosis of patient was subdural hematoma, the signs and radiological findings were not regressed. The patient underwent craniotomy for subdural hematoma. Intraoperatively, dura was a plaque-like thickening and a biopsy was sent to pathology department. After histopathologic and immunohistochemical studies, the case was diagnosed as MALT lymphoma. The patient underwent radiotherapy. Postoperative complication or recurrence was not observed in the follow-up of patient.

Results

Primary central nervous system non-Hodgkin lymphomas (PCNCNHL) are restricted to presentation to the central nervous system (CNS). The frequency of PCNCNHL is 1-3% of all non-Hodgkin lymphomas; in addition, they are 2-4% of all brain neoplasms. They have high incidence in the AIDS population, transplant recipients and immunocompromised patients (1, 2).

Primary and secondary cases of dural lymphomas usually localize at sites rich in meningothelial cells (3,4) and result in a localized mass or a plaque-like thickening of the dura that radiologically resembles other diseases amenable to surgical treatment, such as meningioma (5, 6) or subdural hematoma (4). The surgical excision of the lesion is call for a correct diagnosis.

Conclusions

The early diagnosis and treatment of PDL are important. Histopathologic evaluation is necessary for a correct diagnosis. The magnetic resonance imaging findings cannot differentiate SDH and some dural lesions presented with diffuse skull vault infiltration. Therefore, the surgeons should keep in mind other possibilities in differential diagnosis.

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Case Presentation

Avascular Necrosis of Spine: Case

presentation

Luis Rafael Moscote Salazar MD, Leonardo Dominguez De La Ossa MD, Carlos Alberto Perez Yepes MD (Columbia)

STUDY DESIGN: Avascular necrosis of dorsal and lumbar spine is presented. OBJECTIVES: Avascular necrosis of dorsal and lumbar spine is a rare entity and can be confused with infective and neoplastic processes. We present the role of magnetic resonance imaging (MRI) in the diagnosis of Avascular necrosis .

SUMMARY OF BACKGROUND DATA: Avascular necrosis of vertebral bodies is a known entity; however, involvement of dorsal and lumbar spine is atypical. The imaging features can be confused with an infective etiology, which involves the disc more commonly as compared to Avascular necrosis . Neoplastic destruction of vertebrae also needs to be ruled out in appropriate clinical situations.

METHOD: Frontal and lateral radiographs of the dorsal and lumbar spine were performed followed by an MRI. RESULTS: These radiographic features were correlated with the clinical and pathologic findings. The MRI findings of a wedge-shaped lesion with classic fluid intensity (hyperintense signal, like that of cerebrospinal fluid on T2-weighted images) are characteristic of Avascular necrosis.

CONCLUSIONS: The MRI findings described in this report are very characteristic of Avascular necrosis of spine. Avascular necrosis of dorsal and lumbar spine is often seen in the femoral head, carpals, talus, and humerus, where there is disruption of a single terminal arterial blood supply. Clinical and radiologic correlation could help in making the diagnosis and avoid unnecessary investigations.

♠

Original work

Managing Intracranial Hypertension in Syndromic Craniosynostosis

Guirish A Solanki FRCS(SN) (UK)

Question of Mr Sparrow to Mr G Solanki

I must preface this question with the comment that I have not done this sort of surgery for many years. However the results seem impressive to me, but I'd be interested to see the changes in actual measurements of vertical skull height and AP diameter. This is because the growth of the forehead may simply be an improved ratio of height to AP diameter, consequent on reducing or stopping vertical growth (no longer needed) by augmenting horizontal growth during the phase of rapid head growth. Seeing superimposed outlines highlights the change in calvarial shape, without demonstrating total change in size, unless the scale is the same. Overlays of head shape to the same scale (if, as I suspect, the scale differs) would clarify this point.

Owen Sparrow

Mr Owen Sparrow FRCS
Southampton

Response of Mr Solanki to questions of Mr Sparrow

Dear Owen,

Grateful for the important questions. Enclosed is a response fitting for a neurologist in terms of length for which I beg your forgiveness.

...However the results seem impressive to me:

Thank you for that Owen. Until now we have not had a procedure that virtually increased the skull. This procedure actually increases skull size progressively while laying down new bone in the gap because of the very slow distraction

(0.5mm at a time twice a day). This is similar to the technique of long bone augmentation used by Lizaroff. It is not just to move a piece of bone 1 or 2 cms forward (fronto-orbital advancement and remodelling - FOAR) or backwards (Fixed posterior skull expansion) or sideways (bi-parietal plate release). In this context it is revolutionary in craniofacial surgery. Because it is applied in-situ it creates an equal and opposite force and results in simultaneous frontal distraction increasing the forehead as well! I must confess we did not see this coming...

Each child that has undergone this procedure had raised ICP, papilloedema, dropping centiles on their OFC growth charts some under the 2nd centile from multi-suture or pansynostosis. The clinical improvement is nothing like we have seen before with the other techniques and the children tolerate it much better.

I'd be interested to see the changes in actual measurements of vertical skull height and AP diameter.

All the measurements have been done using Dicom imaging software that provides accurate measurements irrespective of the magnification or image size (they are scaled to size). We have confirmed by 3DCT and MRI the increase in posterior calvarium, posterior fossa and also the maximum AP length increase measured from nasion.

The vertical skull growth, turricephaly, is as you said the side-effect of failure of horizontal head growth as the coronal and lambdoid sutures fuse prematurely. The result is a varying combination of brachy-turrycephaly (the skull can only grow upwards or sideways). In Apert's my theory (supported by empirical evidence) is that brain growth moves forward and upward propelled by focused CSF hydrostatic pressure onto the anterior fontanel (weak spot in the skull at this age) that remains open and increases massively in size in Apert's. In Crouzon's, unfortunately there is pansynostosis and this opportunity for brain growth is denied. So you get brain push towards the other path of least resistance that is the foramen magnum and you get Chiari-type Hindbrain herniation (which you very rarely or never see in Apert's). In fact the forward brain growth in Apert's may be an explanation for the Cervico-medullary kink noted in these children (as the brain is pushed forwards the brain stem no longer remains upright but bends anteriorly).

This is because the growth of the forehead may simply be an improved ratio of height to AP diameter, consequent on reducing or stopping vertical growth (no longer needed) by augmenting horizontal growth during the phase of rapid head growth.

Indeed we want the turricephalic shape to reduce by this distraction and we do see that happening at the level of the coronal suture apex. It does not affect the forehead expansion, which is further anterior and lower down, and this we noted first alongside the posterior occipital expansion. This is why we think that forehead expansion could only occur as a result of Newton's 3rd law(or Mach's interpretation of it) as the distractors are screwed on both sides of the craniotomy cut and the vectorial force although theoretically directed backwards and upwards is actually creating an equal and opposing distracting force on the anterior plate as well, leading to forehead expansion !

Finally none of these changes occur naturally once pansynostosis sets in. The norm is for the brachy-turrycephaly to lead to serious flattening of the forehead with orbital rim underdevelopment.

Seeing superimposed outlines highlights the change in calvarial shape, without demonstrating total change in size, unless the scale is the same.

You are correct in your statement. Our average increase in size has been 26 mm. This was measured from CT scans and plain X-rays performed in every case. About 60 to 70% of this growth has been posterior measured from the posterior clinoid to the posterior-most calvarium and the rest anterior when measured from the nasion. The presentation was based on a wire-frame analysis of the pre and post-op real CT and MR images with solid volume fills. The cartoon-like creation was for highlighting the process. All measurements were done using dicom compliant imaging software in our PACS facility at BCH.

Overlays of head shape to the same scale (if, as I suspect, the scale differs) would clarify this point.

You are again correct. Clinical photography in craniofacial surgery is improving all the time and we have validated this technique for measurement of the cephalic index ratio in sagittal synostosis (SBNS, Manchester 2004, ISPN, Vancouver 2005). While it works well for measurement ratios, it is not as useful for accurate single measurements unless it is digitally scaled. However the sequence has been done to show shape rather than size and the shape does change significantly over the distraction and consolidation phases and then tends to recoil a bit anteriorly once distraction stops.

The radiological, CT and MRI data in other slides also demonstrate these changes (probably more convincingly): That of an increased skull, more rounded shape, more space for the brain and better CSF distribution. More importantly the improved clinical state of the children has been the main reason for considering this procedure.

Kind regards

Guirish

Mr G Solanki FRCSI FRCS(SN)
Birmingham

Response of Mr Sparrow to comment by Mr Solanki

Thank you for a very comprehensive reply, Guirish,

though any change in vertical height hasn't been mentioned: I presume it

is little or none.

Owen

Mr Owen Sparrow FRCS
Southampton

Response of Mr Solanki to comment by Mr Sparrow

Hi Owen,

That is correct. Once the skull height is set because of abnormal differential growth, unless there is a "surgical" reduction the remodelling that occurs following distraction to the skull vault is limited to rounding it rather than significantly reducing the head height.

It tends to halt turricephaly rather than reverse it.

Thank you again.

Guirish

Mr Guirish Solanki FRCSI FRCS(SN)
Birmingham

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