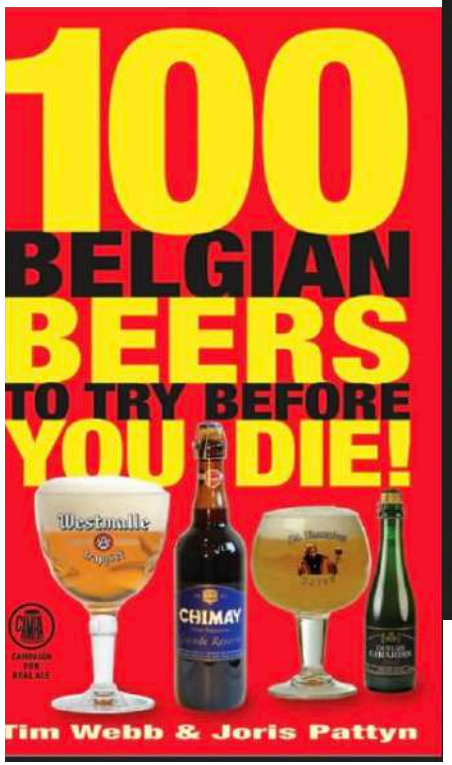
XXXIVe Symposium SIZ-Nursing

»Hors du Coma »

PRISE EN CHARGE DU PATIENT TRAUMATISÉ CRÂNIEN EN COMA

Dr Hugues Maréchal

Est- ce d’importance ?



Traumatisme crânien: définition

- Toute altération de fonction cérébrale ou toute pathologie cérébrale causée par une force externe appliquée à la tête

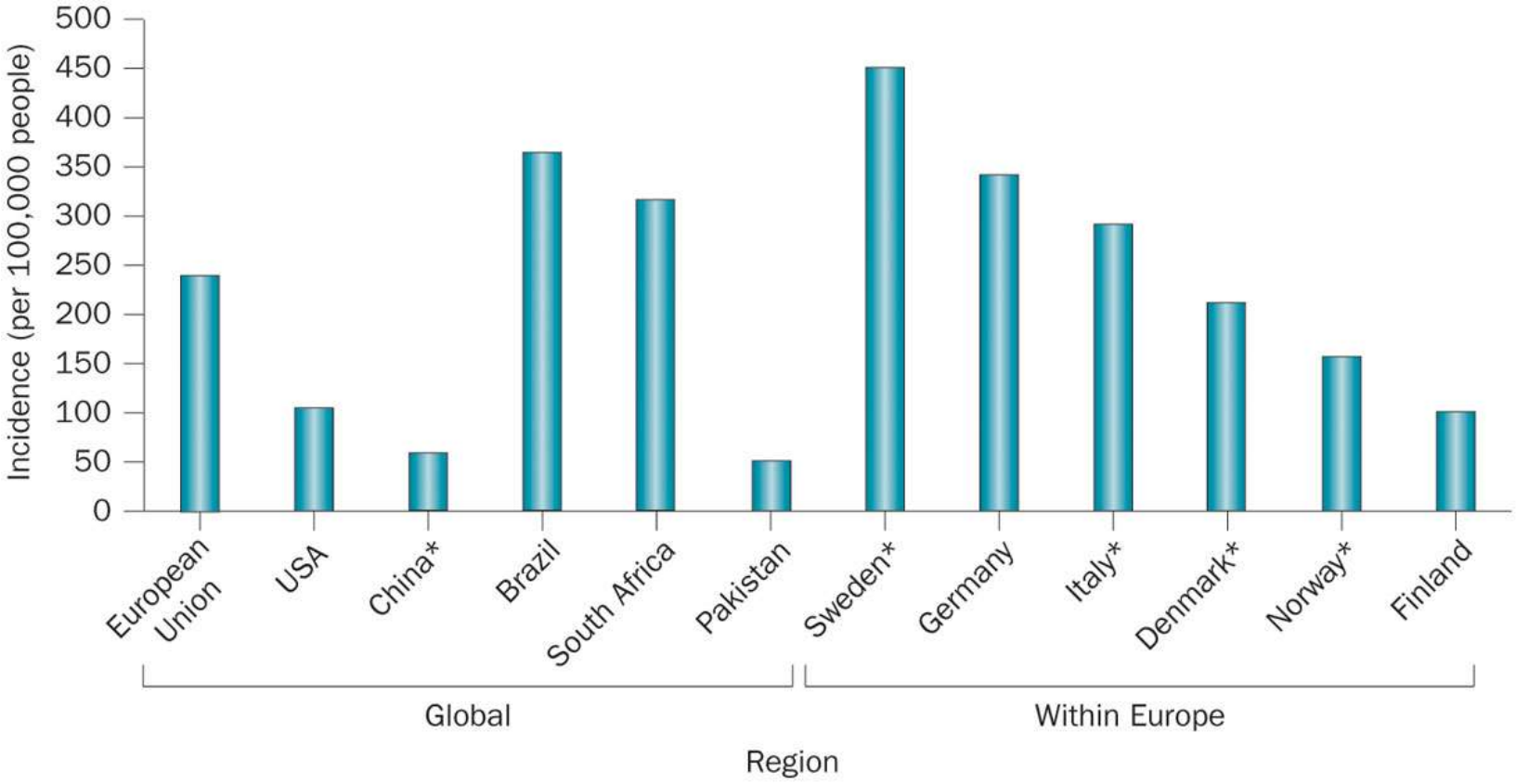
- Pouvant survenir n'importe où, n'importe quand et à n'importe qui, dans des situations telles que les jeux, les accidents, les chutes

- Le résultat est de sévérité variable, allant de la simple commotion au coma

- Et alors classifié comme léger, modéré ou sévère, selon la Glasgow Coma Scale

- Son caractère en est quasi épidémique silencieuse:
  - Aux USA, 1,7 millions de visites aux urgences / an et 280 000 hospitalisations, 52 000 décès/ an

Epidémiologie du TC toutes sévérités



Roozenbeek, B. *et al.* (2013) Changing patterns in the epidemiology of traumatic brain injury
Nat. Rev. Neurol. doi:10.1038/nrneurol.2013.22

Epidémiologie en Europe

- Incidence globale variable, de 47 à 849/100.000 /An, moyenne à 258/100 000

- Mortalité de 9 à 28,10 /100 000 / An

- Age moyen variable de 26,7 à 44,5 selon études

- 28% < 15ans et 18% > 65Ans*

- Touche plus les hommes (55% en Suède, 80% en Irelande)

- Causes : Traffic road accident 26%*, chutes et Violence,

- Où: 35% pdt Loisirs, 30% au domicile, 15% travail *

- Alcool impliqué dans 25% des TC*

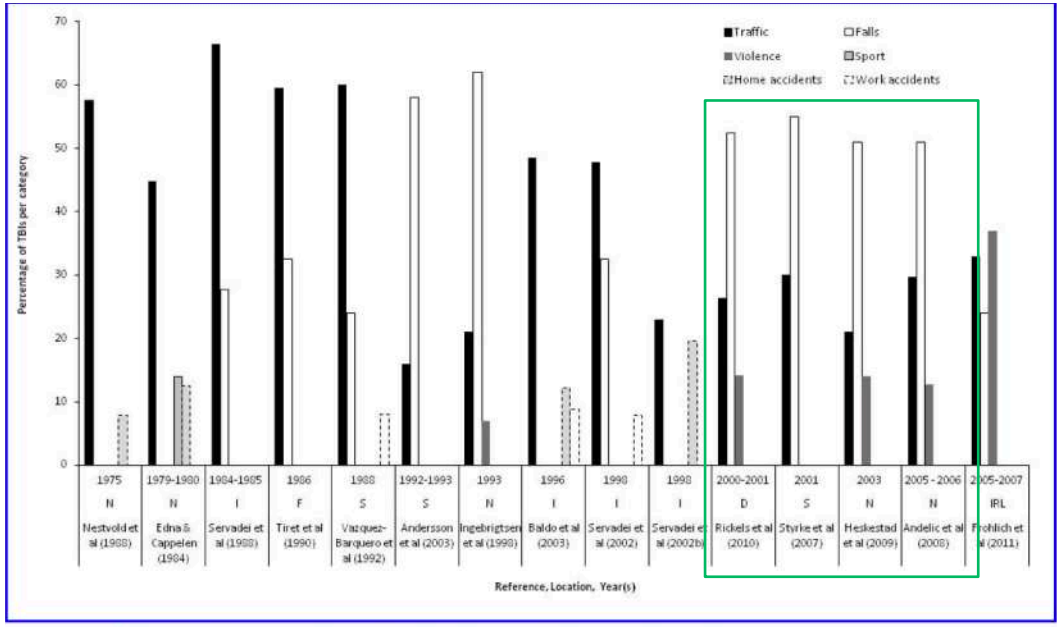


Figure 8 Most common mechanism of injury in regional level studies

Journal of Neurotrauma 2015 Epidemiololgy of TBI in Europe, LSR *ETC

Epidémiologie

Changeante avec le temps et selon le niveau de vie du pays

Table 1 | Age of patients with TBI

Study	Year of study	*n*	Median age (years)	% of patients >50 years
Traumatic Coma Data Bank[44]	1984–1987	746	25	15
UK four-centre study[45]	1986–1988	988	29	27
European Brain Injury Consortium core data survey[46]	1995	847	38	33
Prospective Observational COhort Neurotrauma (POCON)[47]	2008–2009	339	45	43
Austrian severe TBI study[48]	1999–2004	415	48	45
Italian intensive care unit cohort[49]	1997–2007	1,478	45	44

Abbreviation: TBI, traumatic brain injury.

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Epidemiologie: vers une diminution de mortalité?

Table 2 | Outcome over time in observational studies

Study name	Year of study	*n*	Setting	GCS on admission	Mortality	% unfav.	Study
Older observational studies (prior to 1999)							
–	1968–1975	700	UK/NL/US	Coma ≥6 h	51%	62%	Jennett *et al.* (1977)[50]
Traumatic Coma Database (TCDB)	1984–1987	746	US	≤8	39%	58%	Foulkes *et al.* (1991)[44]
UK4 Centre	1986–1988	988	UK	≤8	39%	57%	Murray *et al.* (1999)[45]
European Brain Injury Consortium (EBIC) core data	1995	796 481*	Europe Europe	≤12 ≤8	31% 40%	49% 60%	Murray *et al.* (1999)[46]
Weighted average	–	–	–	–	42%	59%	–
Observational studies (1999–2005)							
Austria	1999–2004	492	Austria	≤8	38%	51%‡	Rusnak *et al.* (2007)[48]
Australasian Traumatic Brain Injury Study (ATBIS)	2000	363	Australia–New Zealand	≤8	32%	55%	Myburgh *et al.* (2008)[51]
–	1999–2004	672	Singapore	≤8	36%	51%	Ng *et al.* (2006)[52]
Weighted average	–	–	–	–	36%	52%	–
More recent studies (2005–2010)							
–	2005–2007	518	Paris	≤8	51%	66%	Darnoux *et al.* (2011)[53]
Prospective Observational COhort Neurotrauma (POCON)	2008–2009	339	NL	≤8	46%	60%	Andriessen *et al.* (2011)[47]
Ontario Prehospital Advance Life Support (OPALS) Major Trauma Study	?	538	Ontario (Canada)	≤8	33%‖	63%‖	Dowling *et al.* (2010)[54]
–	2008–2010	748	Latin America	≤8	31%	54%	Chesnut *et al.* (2011)[55]
Weighted average	–	–	–	–	39%	60%	–

*Severe subset (GCS ≤8 on admission). ‡Unknown in 16%. ‖Outcome assessed at discharge. Abbreviations: GCS, Glasgow Coma Scale; NL, The Netherlands; unfav., unfavourable. Reprinted with permission from *The Lancet*, **380**, Rosenfeld *et al.* Early management of severe traumatic brain injury, 1088–1098, © 2012, with permission from Elsevier.

Chute de mortalité entre 1970 et 1990, de 20à 30% puis stagnation après

Après TC sévère:

- encore 39% de mortalité!
- 60% d'outcome défavorable !!
- 30% ont une bonne récupération (Selon GOS)

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Traumatisme crânien: Caractérisation

Toujours à effectuer selon la séquence suivante:

→Check : Facteurs confondants?
–> Observe : Mvts spontanés
–> Stimulate (paroles, pression (10sec))
-> Rate

Glasgow Coma Scale		
Reponse Oculaire (E) Ouverture des yeux	Réponse Motrice (M)	Réponse Verbale
E4 : spontanée	M6: A la commande	V5: Orientée
E3: A l ’appel	M5: Orientée, Localise la douleur	V4: Confuse (phrase)
E2: A la pression	M4: Retrait, flexion normale	V3: Mots
E1: Absence d’ouverture des yeux	M3: Flexion stéréotypée (décortication)	V2: Sons
	M2: Extension stéréotypée (décérébration)	V1: Absence de sons
	M1: Absence de réponse motrice à la douleurs	

http://glasgowcomascale.org/

Glasgow Coma Scale

Outils d'évaluation neurologique simple et le plus utilisé

Reproductible pour le suivi

Predicteurs outcome

Définit la gravité du traumatisme:

TRAUMATISME CRANIEN			
	Léger	Modéré	Sévère
Glasgow Coma Scale / 15	15-13	12-9	8-3

Coma PosT-Traumatique

Définition:

Caractérisé par l'absence d'éveil et de conscience non réversée par l'application de stimulations.

Etat de non réponse aux stimulations extérieures ou le patient est couché, les yeux fermés, ne pouvant être éveillé et ne pouvant avoir conscience ni de soi ni de l'environnement pour une durée minimale de 1h (afin de faire la différence avec syncope, commotion et autres altérations transitoire de la conscience)

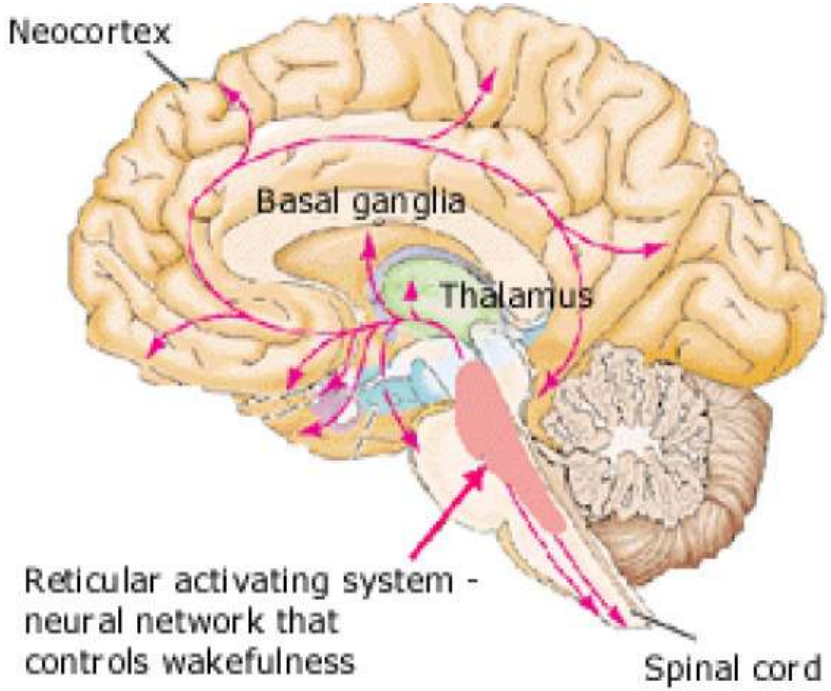
Défini généralement par un GCS <=8/15

Coma post-traumatique

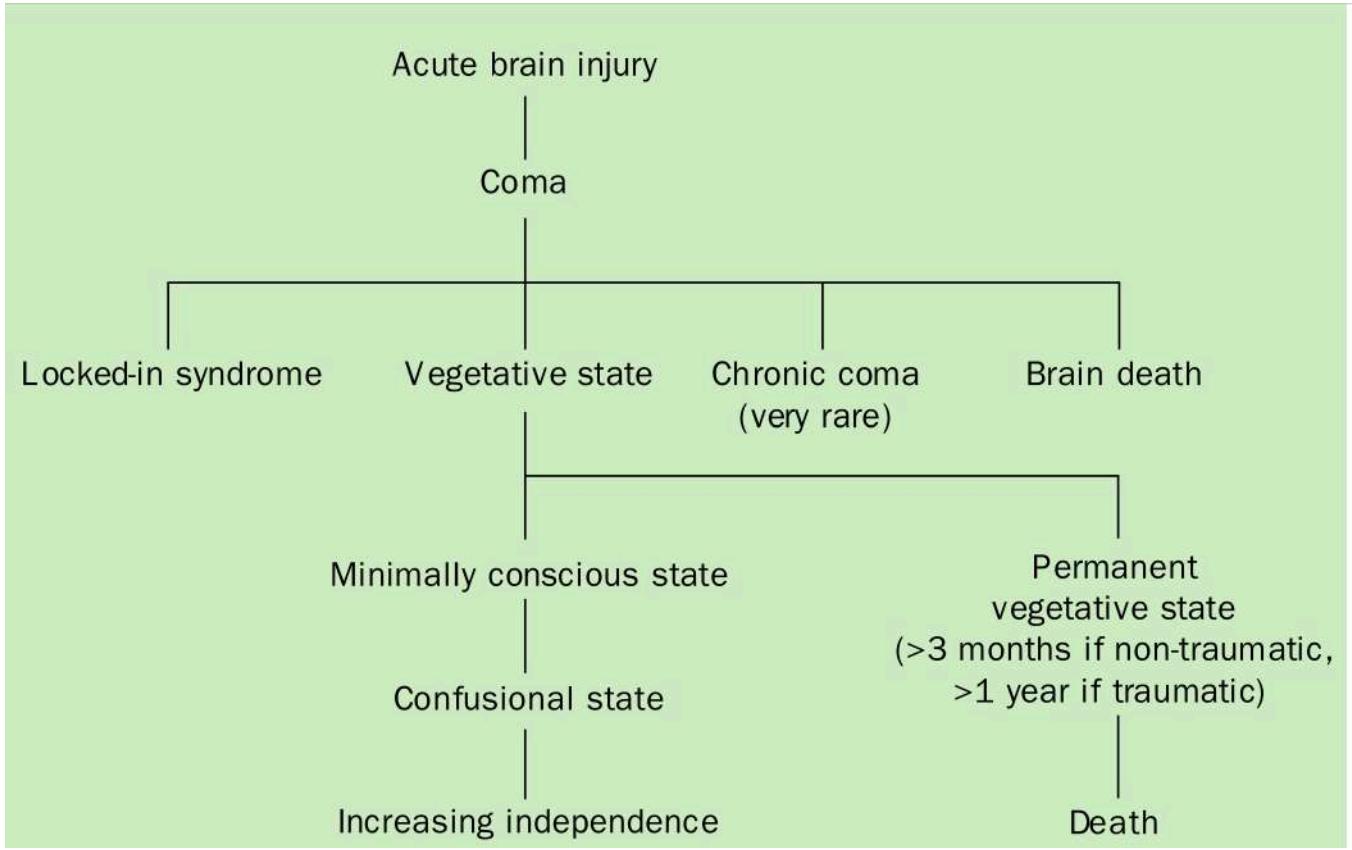
Résulte de dommages :

- Neuronaux, au niveau bihémisphériques corticaux et/ou
- Axonaux , au niveau de la substance blanche et/ou
- Focaux au niveau du tronc cérébral (réticulée ascendante activatrice,.)

Métabolisme cérébral diminué

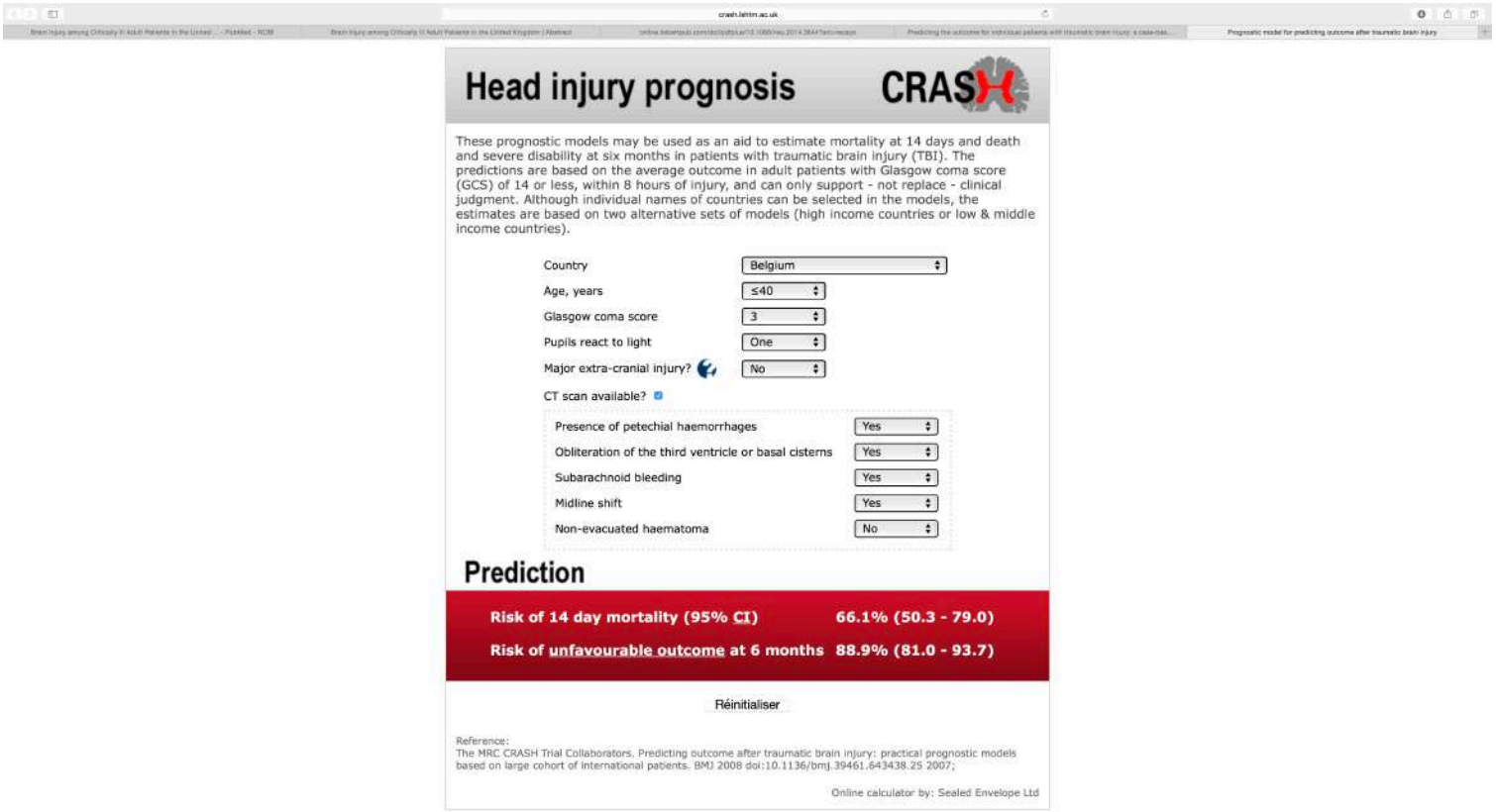


Coma Post-Traumatic



S.laureys, Lancet Neurol 2004

Traumatisme cranien: pronostic



Traumatisme cranien : pronostic

Evaluation pronostic souhaitable (gain temps/ argent / justice distributive/ recherche

Mais

1/ Prédire le pronostic est phase aigue est complexe

2/ Modéles existants ne sont pas utilisable à l'échelle individuelle

3/ Les données dérivées de ces modèles ne peuvent être utilisées pour limiter les interventions en phase aigue mais seulement comme ajout au jugement clinique

4/ ces données ne peuvent-être utilisées

5/ Information à venir provenant de :

- Imagerie (IRM)
- monitoring physiologique (microdialyse,.)
- Génétiques et biomarqueurs

Sont à Intégrer et pourront éventuellemnt etre utiliser à l'avenir pour une médecine de précision

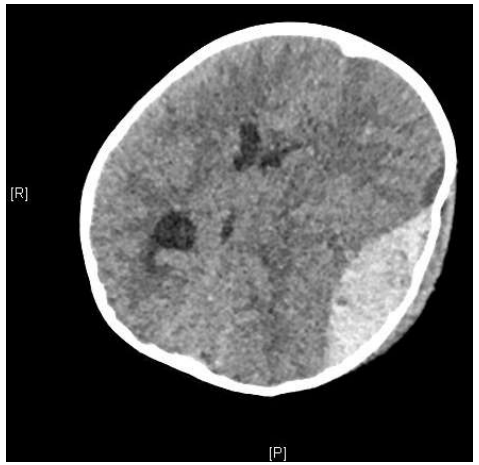
Les soignants doivent offrir un traitement complet et agressif dans la phase précoce après le traumatisme tant que l'outcome n'est pas formellement défini.

Pathophysiologie du Traumatisme crânien

Le traumatisme Cranien est divisé en 2 Phases:

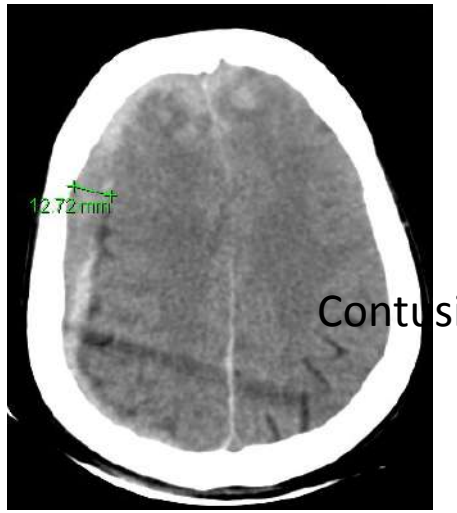
- Phase initiale, déterminant le traumatisme crânien Primaire, résultant directement de la force
  - Hématomes de surface : (1) Extradural (2) sous dural (3) sous arachnoidiens
  - Cisaillement des faisceaux de la substance blanche (DAI) (4)
  - Contusions et hématomes intraparenchymateux (5)
  - Oedeme diffus (6)
  - Lésions vasculaires directes

1/

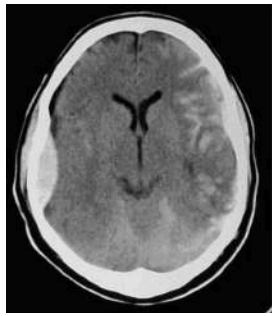


2/

5/

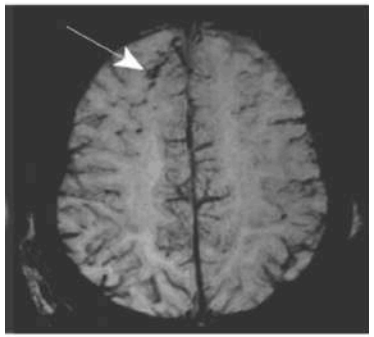


Contusions



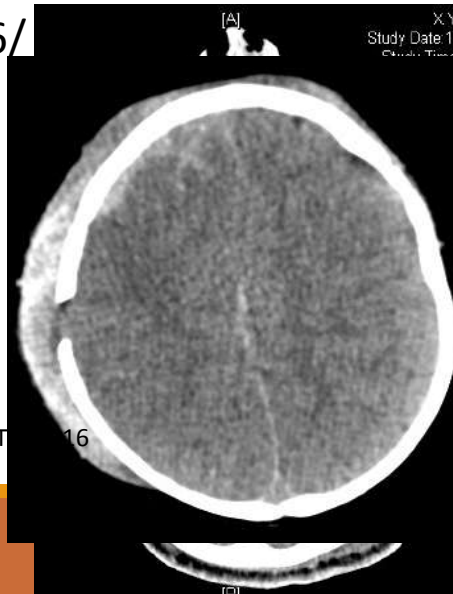
3/

4/



Laskowitz et al, translationnal research in T… 16

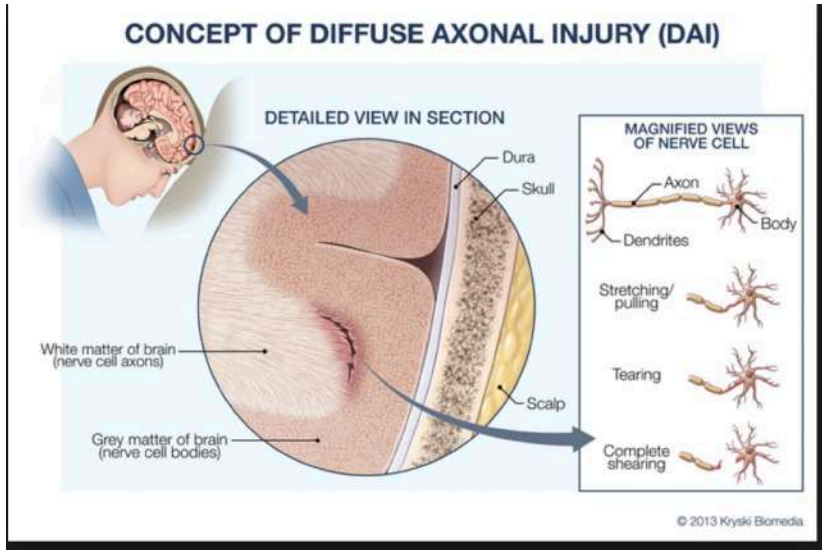
6/



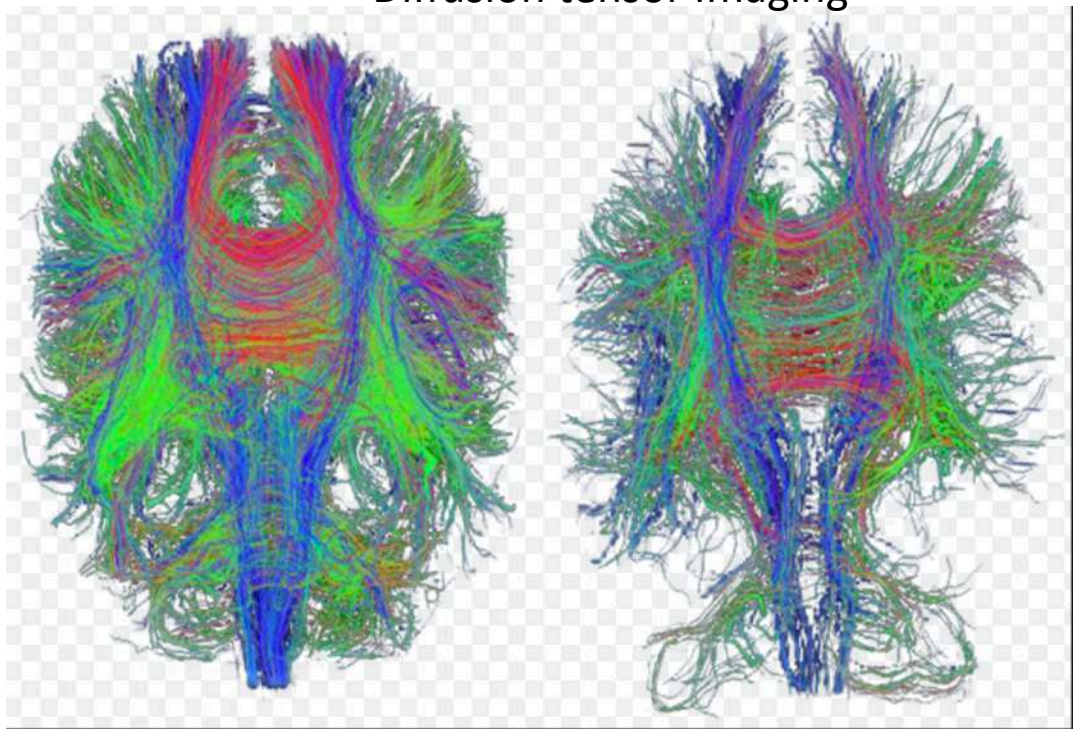
Pathophysiologie

Phase initiale, déterminant le traumatisme crânien Primaire

- Dommage axonal diffus



Diffusion tensor Imaging



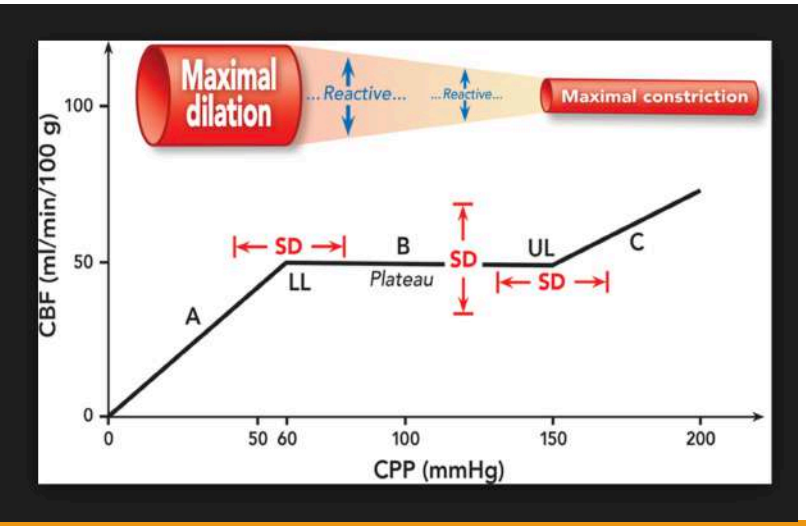
From www.CENTER-TBI.eu

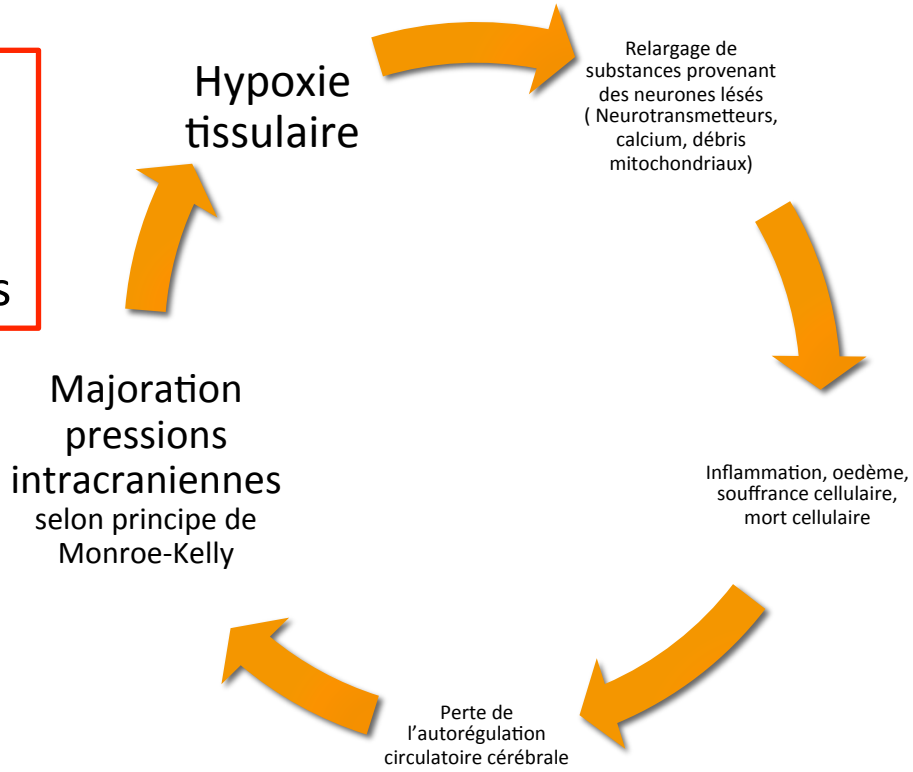
Pas d'action thérapeutique sur phase initiale.
Seule prévention

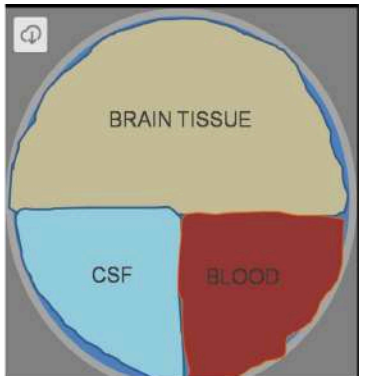
Pathophysiologie

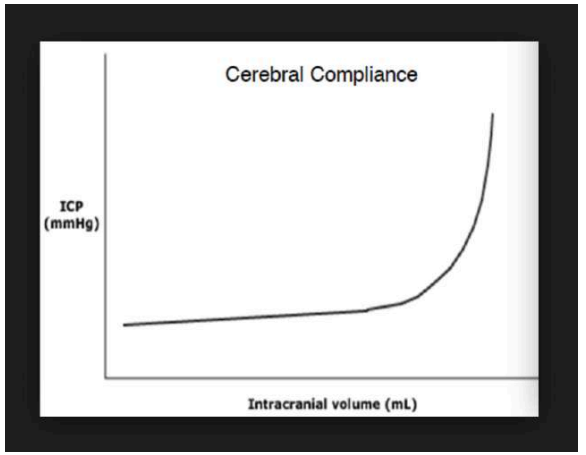
2ePhase = développement des lésions secondaires initiée lors de première phase
Dans les heures - jours après le traumatisme et résulte de mécanismes complexes:

Le tout aggravé par et aggravant:
- Lésions hémorragiques
- La coagulopathie
- Un état de choc sur lésions autres









Prise en charge

BUT: LIMITER LES LESIONS SECONDAIRES

=> First of ALL:

- Airway
- Breathing
- Circulation

A tout prix éviter l'Hypotension et l'Hypoxie

=> Ensuite:

- Réévaluer la fonction neurologique (GCS- Pupilles : taille, symétrie, réactivité – symétrie des mouvements)
- Obtenir un diagnostic
- Permettant la mise en place rapide du traitement définitif
- Ne pas négliger le Management des autres lésions

Prévenir la progression hémorragique

Prise en charge: essentiellement basée sur Guidelines de la Brain Trauma Foundation 2007

1/ Mesures générales :

- Intubation si :
  - GCS <= 8 ou rapide dégradation du GCS
  - Pertes du contrôle de l'airway
  - Hypoxie (PaO_2 < 70mmHg AA) / hypercapnie ($PaCO_2$ > 45mmHg)
- Ventilation Mécanique Invasive pour $PaCO_2$ 36-40 mmHg et PaO_2 80-120mmHg
- Maintien PAM > 80mmHg (si PIC non connue)
- Analgosédation par propfol +/- midazolam, sufenta

Mesures Générales

- Prophylaxie anticomitiale débattue et à mettre en balance (Phénytoine) A considerer particulièrement si traumatisme pénétrant, embarrure, contusions corticales, HSD et HED. SI instaurée, pour 7j
- Contrôle coaguloapthie
- Dossier lit surélevé 30°
- Protection gastrique par ranitdine 50mg 4/j et Alimentation entérale à débuter lentement et à majorer selon tolérance
- Maintien hémoglobine > 9g/dl (seuil non strict, à moduler selon clinique tel hémodynamique, oxygénation compromise, et eventuellement NIRS)
- Correction glycémie par insuline si > 180mg/dL
- Maintien de temperature corporelle entre 36 et 37° C

Prise en charge

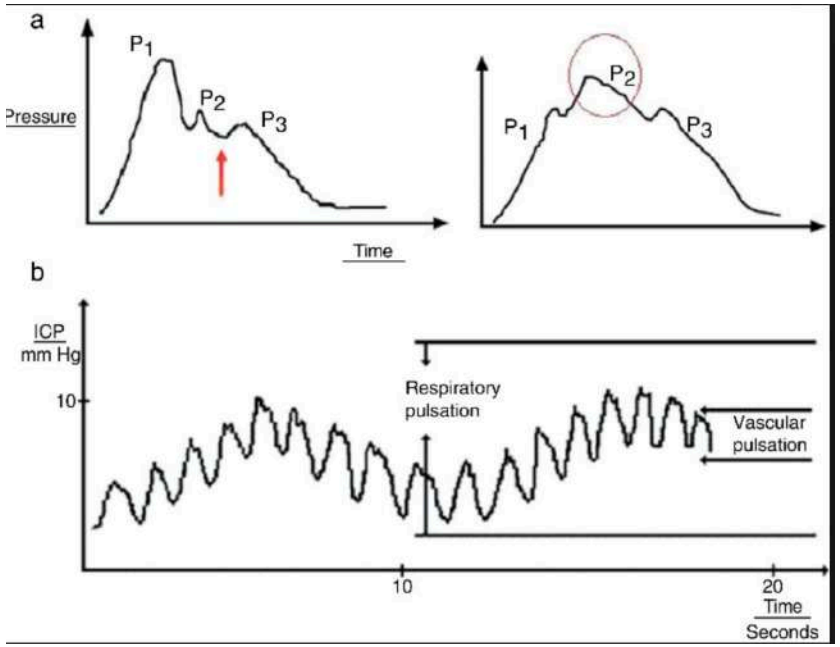
Insertion d'un système de mesure de pression intracranienne si GCS <=8 et :

- CT scan cérébral anormal : p.e. hémorragie, contusions, oedème, signes scannographiques d'Hypertension intracranienne (engagement, citernes de la base comprimées)

- CT scan normal et 2critères ou plus parmi :
  - âge > 40,
  - uni ou bilatéral réponse motrice posturale (M1 à M3)
  - hypotension systémique

- Patient non examinable sur une longue période (chirurgie longue prévue,.)

Prise en charge



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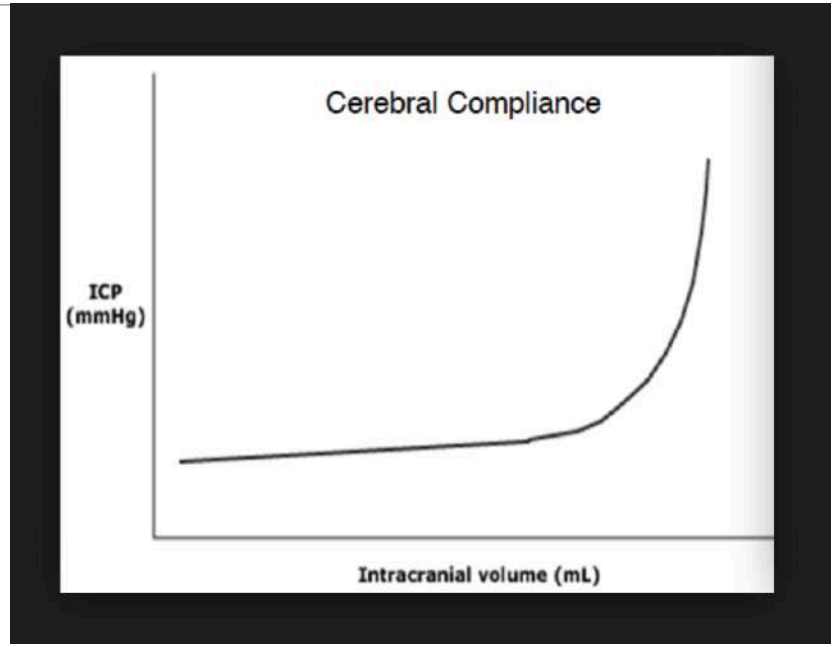

Attention:
Seuil de PIC basé sur faibles données.
Hypoxie cérébrale et dysfonction métabolique peuvent survenir à PIC < 20mmHg
Importance d'intégrer la valeur de PIC dans l'ensemble et aussi de façon dynamique

PIC ?

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A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

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ABSTRACT

BACKGROUND

Intracranial-pressure monitoring is considered the standard of care for severe traumatic brain injury and is used frequently, but the efficacy of treatment based on monitoring in improving the outcome has not been rigorously assessed.

METHODS

We conducted a multicenter, controlled trial in which 324 patients 13 years of age or older who had severe traumatic brain injury and were being treated in intensive care units (ICUs) in Bolivia or Ecuador were randomly assigned to one of two specific protocols: guidelines-based management in which a protocol for monitoring intraparenchymal intracranial pressure was used (pressure-monitoring group) or a protocol in which treatment was based on imaging and clinical examination (imaging–clinical examination group). The primary outcome was a composite of survival time, impaired consciousness, and functional status at 3 months and 6 months and neuropsychological status at 6 months; neuropsychological status was assessed by an examiner who was unaware of protocol assignment. This composite measure was based on performance across 21 measures of functional and cognitive status and calculated as a percentile (with 0 indicating the worst performance, and 100 the best performance).

RESULTS

There was no significant between-group difference in the primary outcome, a composite measure based on percentile performance across 21 measures of functional and cognitive status (score, 56 in the pressure-monitoring group vs. 53 in the imaging–clinical examination group; P=0.49). Six-month mortality was 39% in the pressure-monitoring group and 41% in the imaging–clinical examination group (P=0.60). The median length of stay in the ICU was similar in the two groups (12 days in the pressure-monitoring group and 9 days in the imaging–clinical examination group; P=0.25), although the number of days of brain-specific treatments (e.g., administration of hyperosmolar fluids and the use of hyperventilation) in the ICU was higher in the imaging–clinical examination group than in the pressure-monitoring group (4.8 vs. 3.4, P=0.002). The distribution of serious adverse events was similar in the two groups.

CONCLUSIONS

For patients with severe traumatic brain injury, care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT01068522.)

From the Departments of Neurological Surgery (R.M.C., N.T., S.D., J.P., J.B., K.C., J.M.C.), Orthopaedics and Sports Medicine (R.M.C.), Biostatistics (N.T.), and Rehabilitation Medicine (S.D., J.M.), University of Washington, Harborview Medical Center, Seattle; the Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland (N.C.); Hospital de Emergencias Dr. Clemente Alvarez, Santa Fe (C.R., G.P., S.L.), and Hospital Nacional Professor Alejandro Posadas, Buenos Aires (W.V.) — both in Argentina; and the Departments of Psychiatry (M.C.) and HIV Neurobehavioral Research Programs (T.H.), University of California, San Diego, La Jolla. Address reprint requests to Dr. Chesnut at the University of Washington, Harborview Medical Center, Department of Neurological Surgery, 325 Ninth Ave., Box 359766, Seattle, WA 98104, or at chesnutr@uw.edu.

*Members of the Global Neurotrauma Research Group are listed in the Supplementary Appendix, available at NEJM.org.

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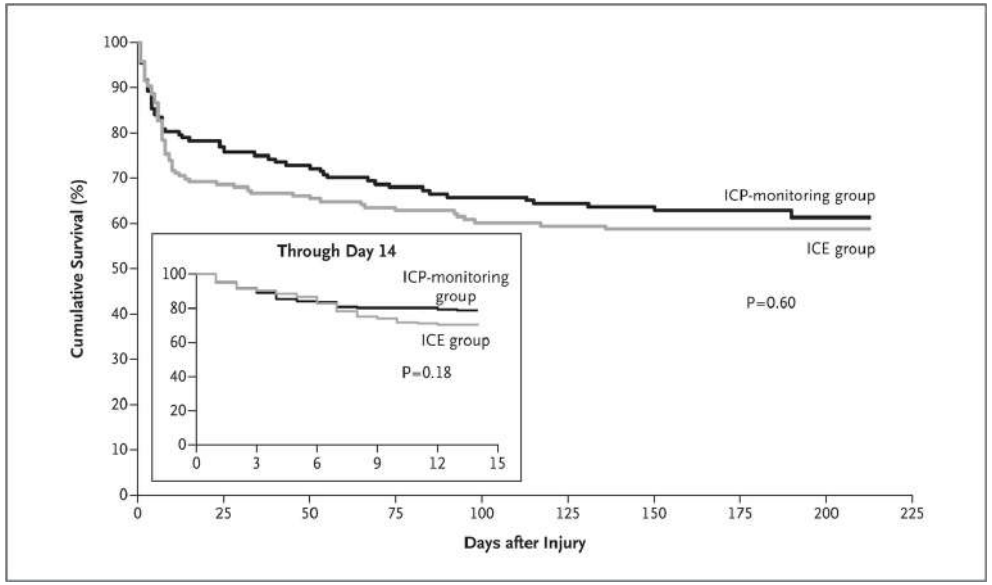


Prise en charge

Maintenir

- PPC > 60mmHg toujours par :
  - Volémisation (Plasmalyte A) selon monitoring HD (DeltaPP, Passive leg raisng, fluid challenge, PiCCO)
  - Noradrénaline
- Et PIC < = 20

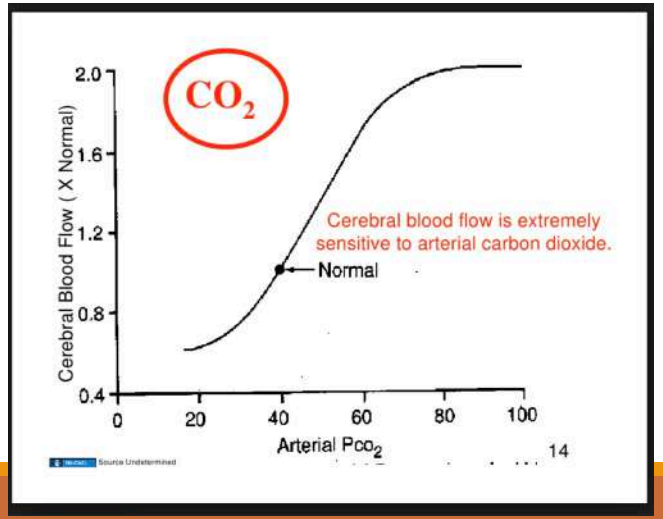
Si PIC > 20mmHg => diminuer le volume de composant IntraCérébraux

- 1/ drainage de LCR et de toute lésion (hématome,.)
- 2/ Osmothérapie, Agissant par appel d'eau au travers de la BHE par :
  - NaCl Hypertonique (20%, 3%,.. Selon protocole local) , à renouveler si nécéssaire si Na+ < 155mEq/L sur gazométrie artérielle
  - Mannitol 0.25 à 1g/kg /6h avec mesure osmolarité sanguine, à maintenir < 320mOsmol

Prise en charge

SI PIC > 20mmHg de manière réfractaire :

- Considérer contrôle CT scanner cérébral de contrôle (Saignement, Ischémie,..) => MASSE Evacuable??
- Considérer curarisation et alourdissement de la sédation
- Contrôle EEG pour exclure activité épileptique infraclinique ; Si non exclue (impossibilité de faire l'EEG) ou présente, prophylaxie antiépileptique pour les 7ers jours par diphantoine ou keppra
- Hypothermie légère (35-36°C)
- Hypocapnie par Pallier: 34-36mmHg, 28-32mmhg(avec contrôle Doppler Trans Cranien souhaitable) et envisager mesure d'oxygénation cérébrale:
  - Sonde tissulaire
  - SJO2
  - NIRS



Prise en charge

Si PIC réfractaire > 20mmHg aux mesures précédentes :

- 1/ Envisager Craniectomie en discussion avec neurochirurgien
- Mais etude ci-contre problématique, non- real life, basée sur seuil inavriable de PIC 20mmHg

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Decompressive Craniectomy in Diffuse Traumatic Brain Injury

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ABSTRACT

BACKGROUND

It is unclear whether decompressive craniectomy improves the functional outcome in patients with severe traumatic brain injury and refractory raised intracranial pressure.

METHODS

From December 2002 through April 2010, we randomly assigned 155 adults with severe diffuse traumatic brain injury and intracranial hypertension that was refractory to first-tier therapies to undergo either bifrontotemporoparietal decompressive craniectomy or standard care. The original primary outcome was an unfavorable outcome (a composite of death, vegetative state, or severe disability), as evaluated on the Extended Glasgow Outcome Scale 6 months after the injury. The final primary outcome was the score on the Extended Glasgow Outcome Scale at 6 months.

RESULTS

Patients in the craniectomy group, as compared with those in the standard-care group, had less time with intracranial pressures above the treatment threshold (P<0.001), fewer interventions for increased intracranial pressure (P<0.02 for all comparisons), and fewer days in the intensive care unit (ICU) (P<0.001). However, patients undergoing craniectomy had worse scores on the Extended Glasgow Outcome Scale than those receiving standard care (odds ratio for a worse score in the craniectomy group, 1.84; 95% confidence interval [CI], 1.05 to 3.24; P=0.03) and a greater risk of an unfavorable outcome (odds ratio, 2.21; 95% CI, 1.14 to 4.26; P=0.02). Rates of death at 6 months were similar in the craniectomy group (19%) and the standard-care group (18%).

CONCLUSIONS

In adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavorable outcomes. (Funded by the National Health and Medical Research Council of Australia and others; DECRA Australian Clinical Trials Registry number, ACTRN012605000009617.)

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*Investigators in the Decompressive Craniectomy (DECRA) trial are listed in the Supplementary Appendix, available at NEJM.org.

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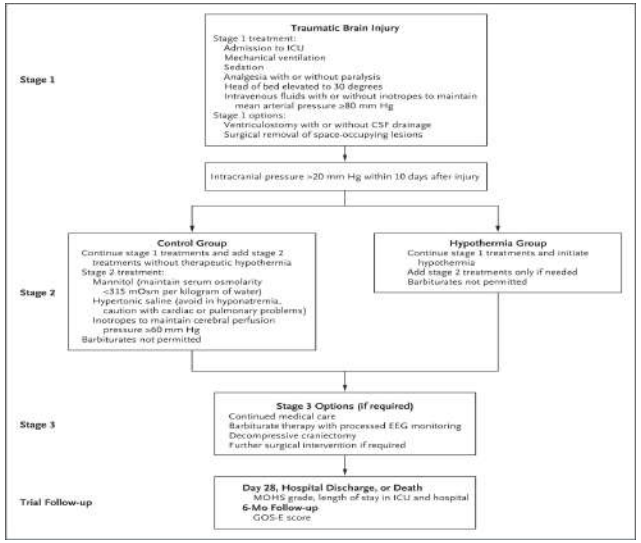
Prise en charge

Si indication de Craniectomie réfutée

- Hypothermie 32-35 ° C
- Hypocapnie 25-29 transitoire avec mesure oxygénation cérébrale , contrôle Doppler Trans Cranien souhaitable
- Suppression méatbolique cérébrale sous controle EEG (= Coma barbiturique)



The NEW ENGLAND JOURNAL of MEDICINE

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Hypothermia for Intracranial Hypertension after Traumatic Brain Injury

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ABSTRACT

BACKGROUND

In patients with traumatic brain injury, hypothermia can reduce intracranial hypertension. The benefit of hypothermia on functional outcome is unclear.

METHODS

We randomly assigned adults with an intracranial pressure of more than 20 mm Hg despite stage 1 treatments (including mechanical ventilation and sedation management) to standard care (control group) or hypothermia (32 to 35°C) plus standard care. In the control group, stage 2 treatments (e.g., osmotherapy) were added as needed to control intracranial pressure. In the hypothermia group, stage 2 treatments were added only if hypothermia failed to control intracranial pressure. In both groups, stage 3 treatments (barbiturates and decompressive craniectomy) were used if all stage 2 treatments failed to control intracranial pressure. The primary outcome was the score on the Extended Glasgow Outcome Scale (GOS-E; range, 1 to 8, with lower scores indicating a worse functional outcome) at 6 months. The treatment effect was estimated with ordinal logistic regression adjusted for prespecified prognostic factors and expressed as a common odds ratio (with an odds ratio <1.0 favoring hypothermia).

RESULTS

We enrolled 387 patients at 47 centers in 18 countries from November 2009 through October 2014, at which time recruitment was suspended owing to safety concerns. Stage 3 treatments were required to control intracranial pressure in 54% of the patients in the control group and in 44% of the patients in the hypothermia group. The adjusted common odds ratio for the GOS-E score was 1.53 (95% confidence interval, 1.02 to 2.30; P=0.04), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 26% of the patients in the hypothermia group and in 37% of the patients in the control group (P=0.03).

CONCLUSIONS

In patients with an intracranial pressure of more than 20 mm Hg after traumatic brain injury, therapeutic hypothermia plus standard care to reduce intracranial pressure did not result in outcomes better than those with standard care alone. (Funded by the National Institute for Health Research Health Technology Assessment program; Current Controlled Trials number, ISRCTN34555414.)

From the Centre for Clinical Brain Sciences (P.J.D.A.), Department of Anaesthesia, Critical Care, and Pain Medicine (H.L.S., B.A.H., C.G.B., J.K.J.R.), and Centre for Population Health Sciences (A.R., G.D.M.), University of Edinburgh, and Critical Care, Western General Hospital, NHS Lothian (B.A.H., J.K.J.R.) — all in Edinburgh. Address reprint requests to Dr. Andrews at Ward 20, Intensive Care Unit, Western General Hospital, Crewe Rd., Edinburgh EH4 2XU, United Kingdom, or at p.andrews@ed.ac.uk.

*A complete list of investigators in the European Study of Therapeutic Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial) is provided in the Supplementary Appendix, available at NEJM.org.

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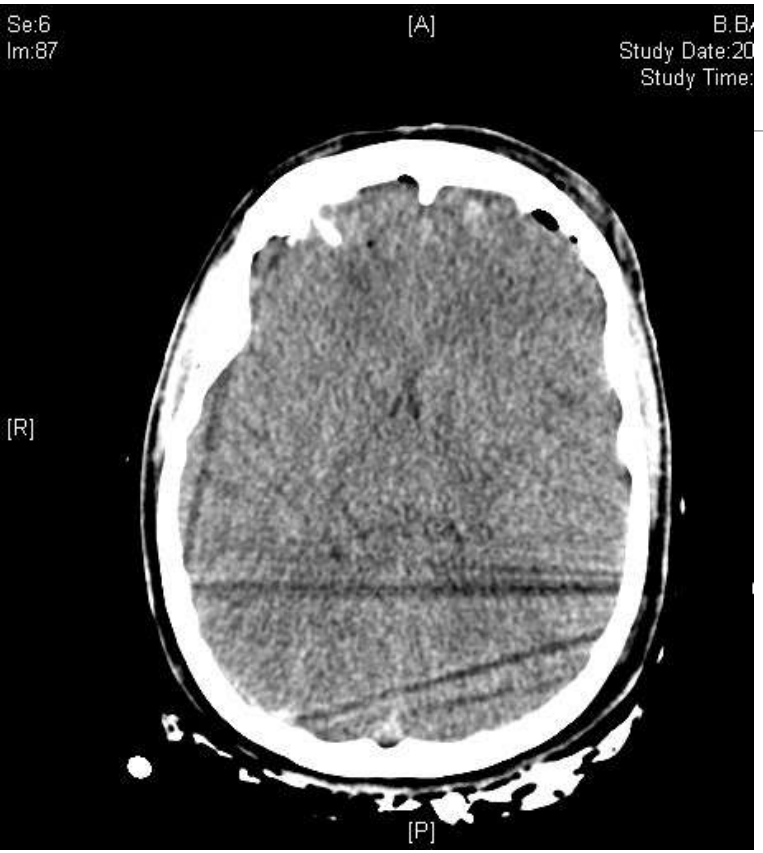
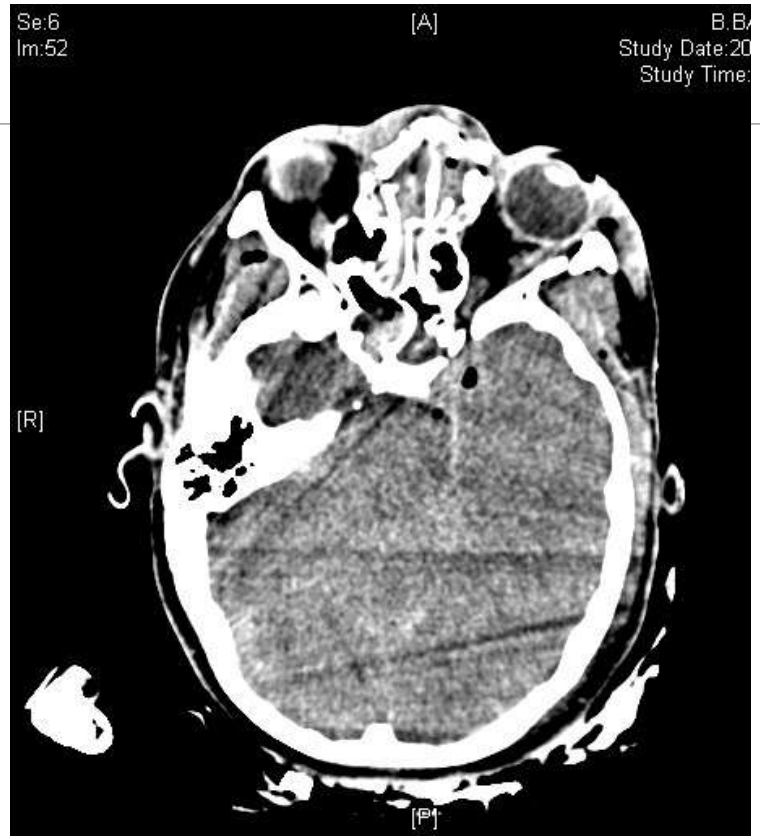
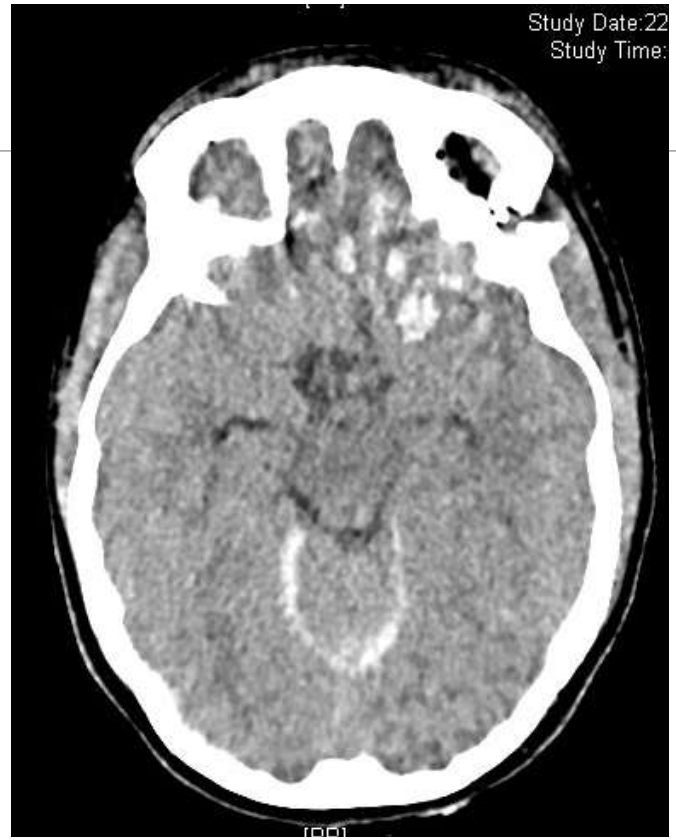
DOI: 10.1056/NEJMoa1507581

Cas clinique 1: femme 19ans, passagère, choc frontal



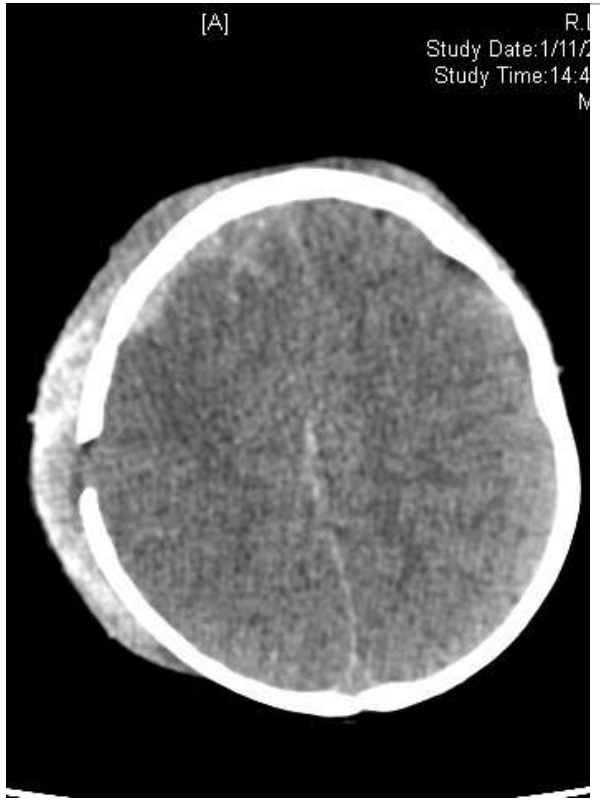




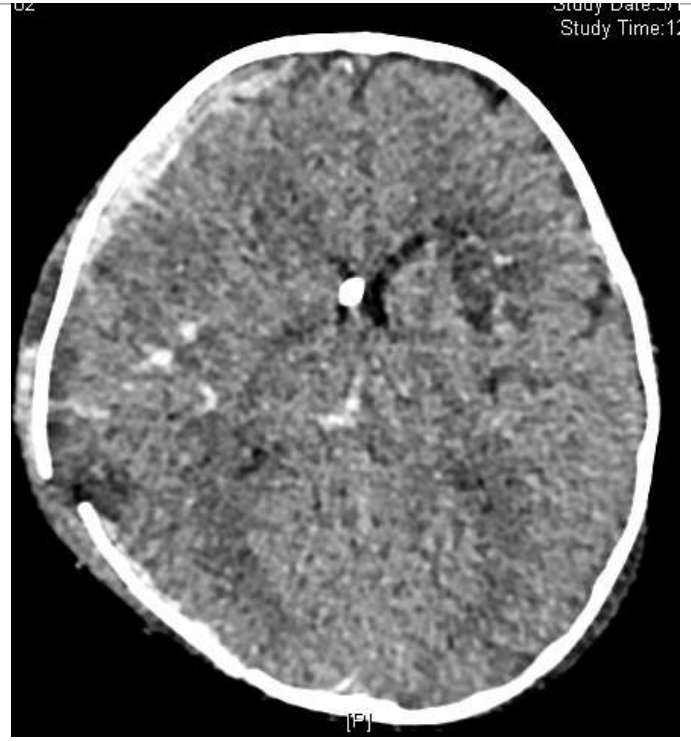
J2

GCS 4/15 initial puis 6/15 après réanimation initiale
Evolution Coma => VS => MCS

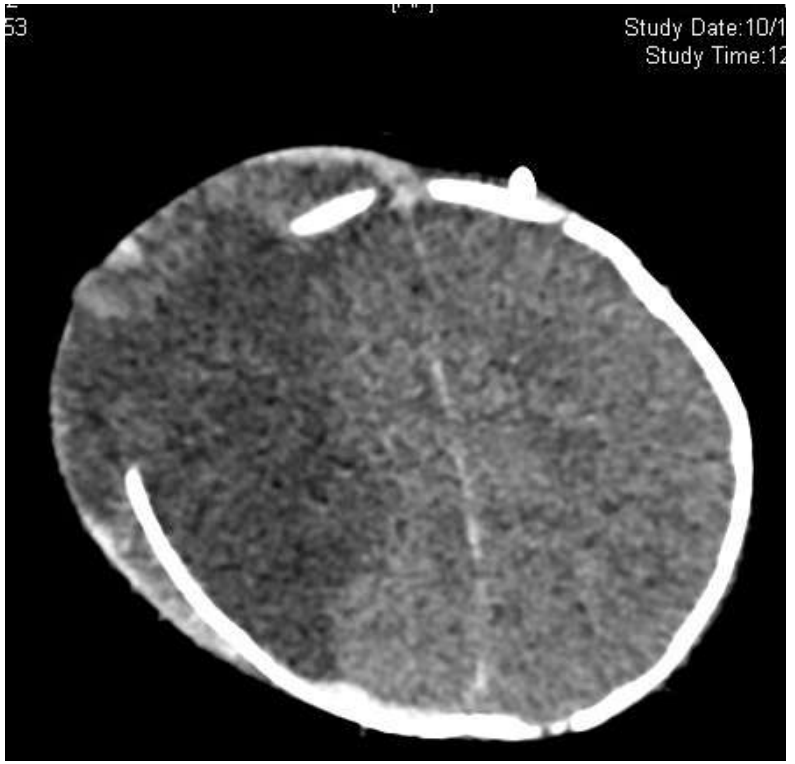
Cas Clinique 2: Fille de 2 ans, chute de hauteur 2m



GCS initial E2V2M5, développement rapide d'une mydriase uni puis bilatérale
Pose d'une DVE en urgence. PIC 70

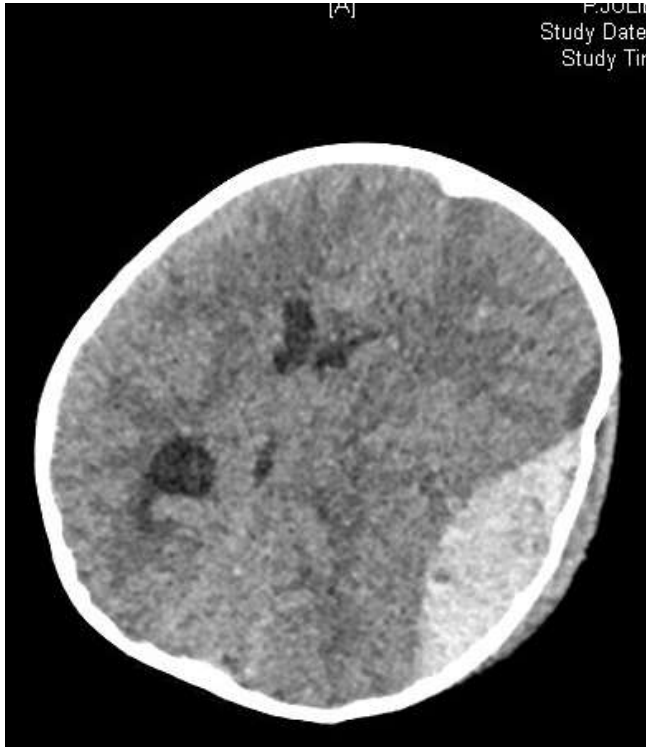


PIC controlée rapidement mais moyennant 3e pillier

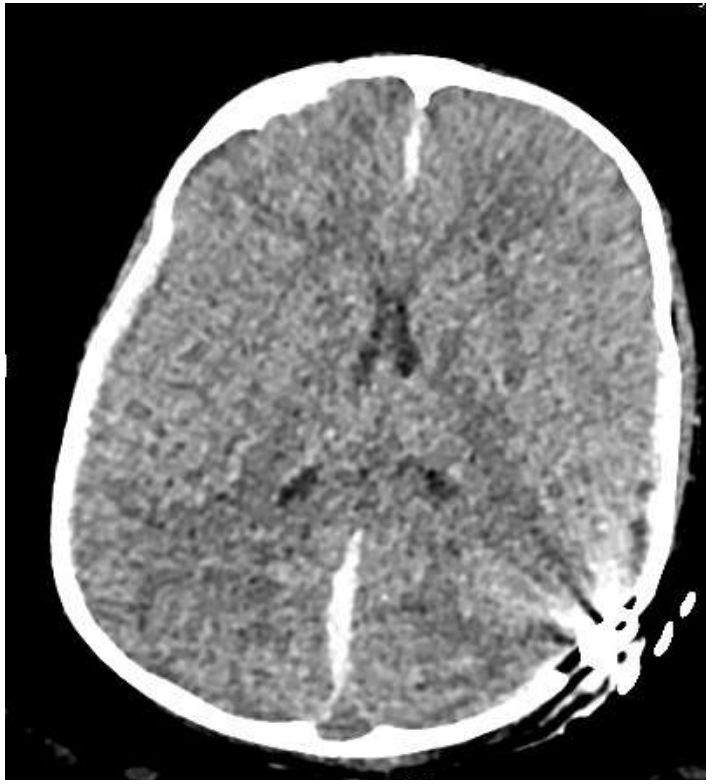


Outcome défavorable, herniation cérébrale

Cas clinique 3: fille 7ans, chute de sa hauteur, sous anticoagulation

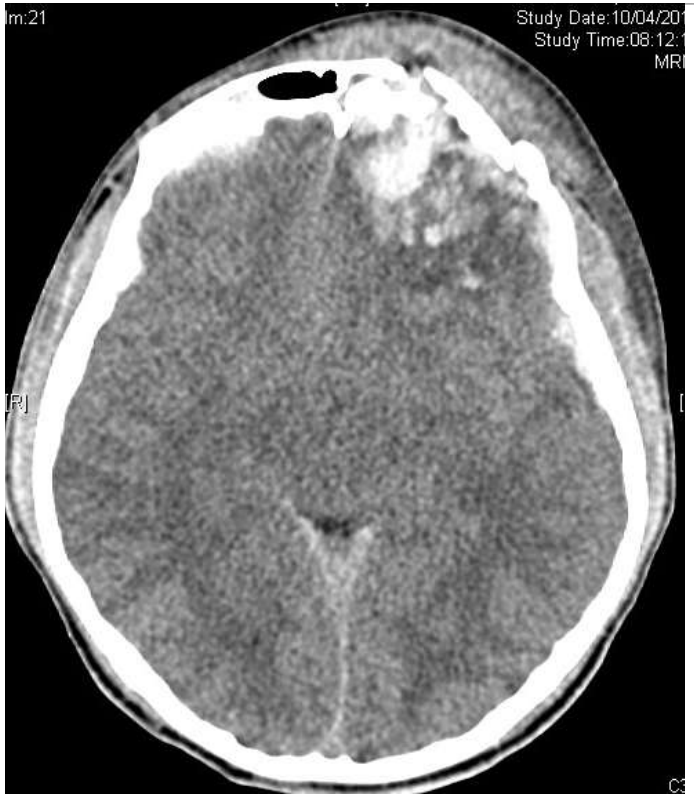


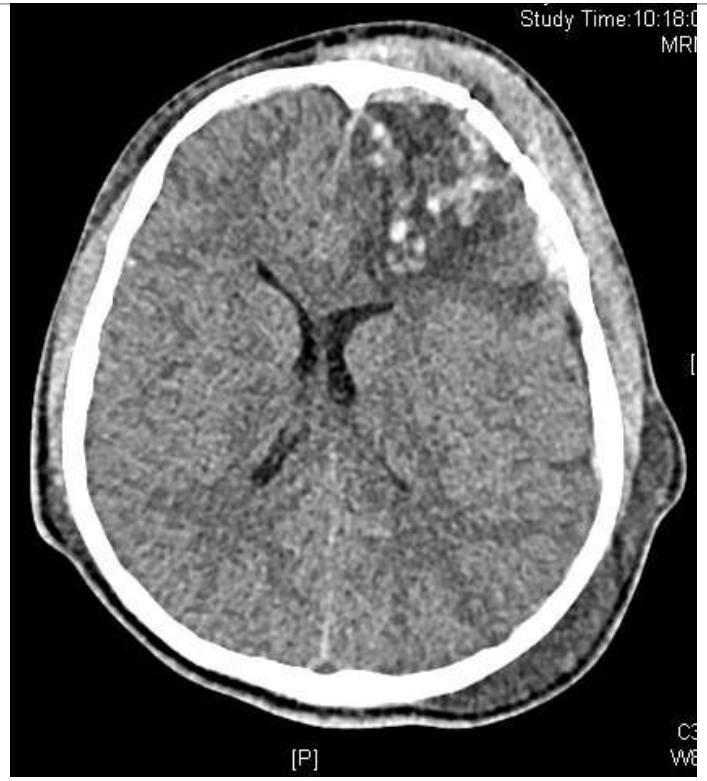
Admise secondairement.
Tableau d'engagement à l'admission
Stabilisation, osmothérapie et OP en urgence dans les 30min de son admission



Sortie USI au 5e jour, sans déficit majeur

Cas clinique 4: Garcon, 14ans, chute 10m, réception frontale.





Intubé pour agitation, désorienté mais parlant à son admission E3V4M5

Conclusion

Le traumatisme Cranien est une pathologie extrêmement lourde pour les patients, leur famille et la société

La prise en charge aigue se doit d'etre aggressive afin de limiter les lésions secondaires

Peu de recommendations fortes guident nos thérapeutiques actuellement mais surtout en raison d'un design optimalisable

Besoins d'un autre type d'etude, real-life

Etudes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Clinical Trial of Progesterone for Severe Traumatic Brain Injury

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ABSTRACT

BACKGROUND

Progesterone has been associated with robust positive effects in animal models of traumatic brain injury (TBI) and with clinical benefits in two phase 2 randomized, controlled trials. We investigated the efficacy and safety of progesterone in a large, prospective, phase 3 randomized clinical trial.

METHODS

We conducted a multinational placebo-controlled trial, in which 1195 patients, 16 to 70 years of age, with severe TBI (Glasgow Coma Scale score, ≤8 [on a scale of 3 to 15, with lower scores indicating a reduced level of consciousness] and at least one reactive pupil) were randomly assigned to receive progesterone or placebo. Dosing began within 8 hours after injury and continued for 120 hours. The primary efficacy end point was the Glasgow Outcome Scale score at 6 months after the injury.

RESULTS

Proportional-odds analysis with covariate adjustment showed no treatment effect of progesterone as compared with placebo (odds ratio, 0.96; confidence interval, 0.77 to 1.18). The proportion of patients with a favorable outcome on the Glasgow Outcome Scale (good recovery or moderate disability) was 50.4% with progesterone, as compared with 50.5% with placebo. Mortality was similar in the two groups. No relevant safety differences were noted between progesterone and placebo.

CONCLUSIONS

Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials. (Funded by BHR Pharma; SYNAPSE ClinicalTrials.gov number, NCT01143064.)