TESIS DOCTORAL

El eje Hipotalámico-Hipofisario-Suprarrenal en el paciente crítico

AUTOR: Juan Antonio Llompart Pou

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Departament de Biologia Fonamental i Ciències de la Salut

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Tesis presentada por **Juan Antonio Llompart Pou** para optar al grado de Doctor

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Índice

Abreviaturas

ACTH: Hormona adrenocorticotropa.

CIRCI: Critical Illness-Related Corticosteroid Insufficiency.

CRH: Hormona liberadora de corticotropina.

GC: Glucocorticoide/s.

GTC: globulina transportadora de cortisol.

HDCST: high-dose corticotropin stimulation test.

HHS: hipotalámico-hipofisario-suprarrenal.

ISR: Insuficiencia suprarrenal relativa.

LDST: Low-dose steroid therapy.

RGC: Receptor glucocorticoide.

SOFA: Sepsis-related Organ Failure Assesment.

TCE: Traumatismo craneoencefálico.

UCI: Unidad de Cuidados Intensivos.

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1. Low dose steroid therapy does not affect hemodynamic response in septic shock patients. Raurich JM, Llompart-Pou JA, Ibáñez J, Frontera G, Pérez O, García de Carlos L, Ayestarán JI. ***J Crit Care 2007; 22:324-9.***
2. Respuesta hemodinámica precoz a los corticoides en el shock séptico. Llompart-Pou JA, Raurich JM, Ibáñez J, Riesco M, Ayestarán JI. ***Med Intensiva 2008; 32:385-90.***
3. Relationship between plasma adrenocorticotropin hormone and intensive care unit survival in early traumatic brain injury. Llompart-Pou JA, Raurich JM, Ibáñez J, Burguera B, Ayestarán JI, Pérez-Bárcena J. ***J Trauma 2007; 62:1457-61***.
4. Acute HPA response in traumatic brain injury with and without extracerebral trauma. Llompart-Pou JA, Raurich JM, Pérez-Bárcena J, Barceló A, Ibáñez J, Ayestarán JI. ***Neurocrit Care 2008; 9:230-6***.
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1. Introducción

1.1. Fisiopatología del eje hipotalámico-hipofisario suprarrenal

El cortisol es el glucocorticoide (GC) principal en el humano y se secreta a nivel de la glándula suprarrenal. En personas sanas, es producido tras la estimulación por la hormona adrenocorticotropa (ACTH, ver Figura 1), que se libera en la hipófisis tras ser estimulada, a su vez, desde el hipotálamo por la hormona liberadora de corticotropina (CRH). Estas dos hormonas están sometidas a un mecanismo de retroalimentación negativo por el cortisol circulante. Además, este sistema se encuentra estrechamente ligado al sistema inmunológico, que ejerce asimismo acciones estimulantes y supresoras del eje hipotalámico-hipofisario-suprarrenal (HHS) a través de las citoquinas pro y antiinflamatorias. De este modo, se obtiene una liberación de cortisol que sigue un ritmo circadiano con pico durante la mañana (Cooper, 2003; Mesotten, 2008). La vida media circulante es de 70-120 minutos, su semivida biológica de aproximadamente 6-8 horas y su precursor fundamental es el colesterol (Marik, 2009).

El cortisol circulante se encuentra ligado en su mayor parte a la globulina transportadora de cortisol (GTC), y en menor medida a la albúmina. La fracción libre de cortisol, que es la biológicamente activa, constituye menos del 10% del cortisol total (Cooper, 2003; Mesotten, 2008, Lamberts, 1997). El cortisol pasa desde el plasma al espacio intersticial, y desde allí, a la célula (ver Figura 2), donde a través del sistema enzimático de la 11β-hidroxiesteroide deshidrogenasa, se une y activa al receptor glucocorticoide (RGC), de localización citoplasmática, que se encuentra unido a las proteínas "heat

shock" e inactivo. Entonces, se producen diversos cambios estructurales, y el complejo GC-RGC se libera de las proteínas "heat shock" y se trasloca al núcleo de la célula. Los mecanismos por los que el RGC interfiere con la transcripción de mediadores proinflamatorios son la unión a zonas específicas del DNA y la interacción con varios factores de transcripción nuclear. Todo ello resulta en un significativo aumento en la actividad celular GC, que constituye un componente esencial en la adaptación al estrés y en el mantenimiento de la homeostasis celular y orgánica (Prignent, 2004; Cohen, 2009).

La aldosterona, también secretada en la glándula suprarrenal, es el mineralocorticoide principal en el hombre. Sin embargo, su secreción es regulada fundamentalmente por el sistema renina-angiotensina y los niveles plasmáticos de potasio, y también juega un papel fundamental en la homeostasis (Findling, 1987; Lamberts, 1997).

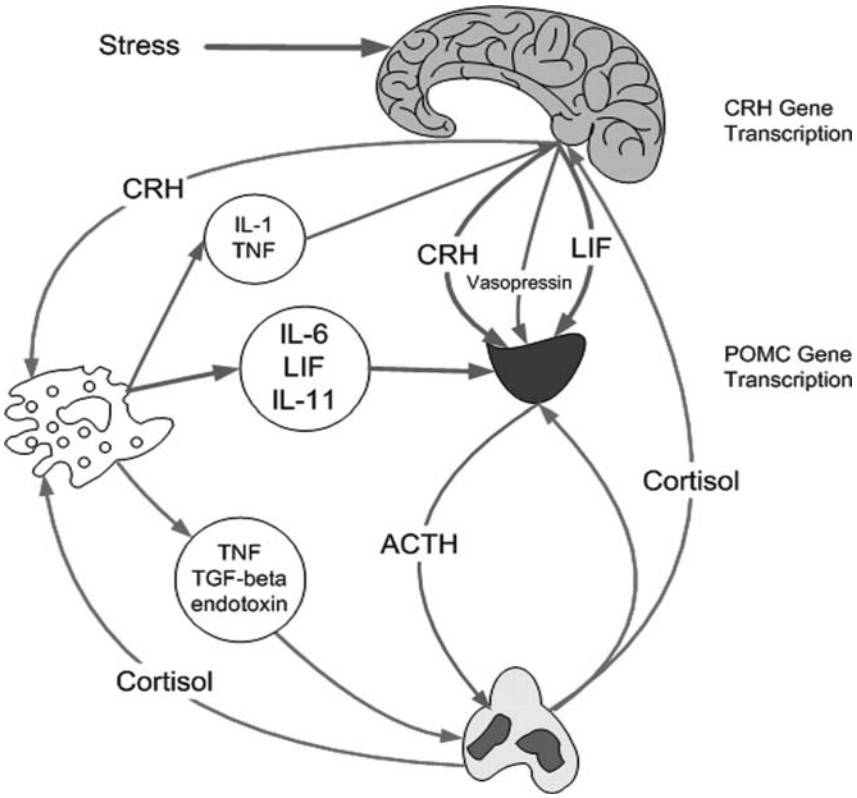

Figura 1. *Activación del eje HHS y su relación con la respuesta inflamatoria (Marik, 2008)*.

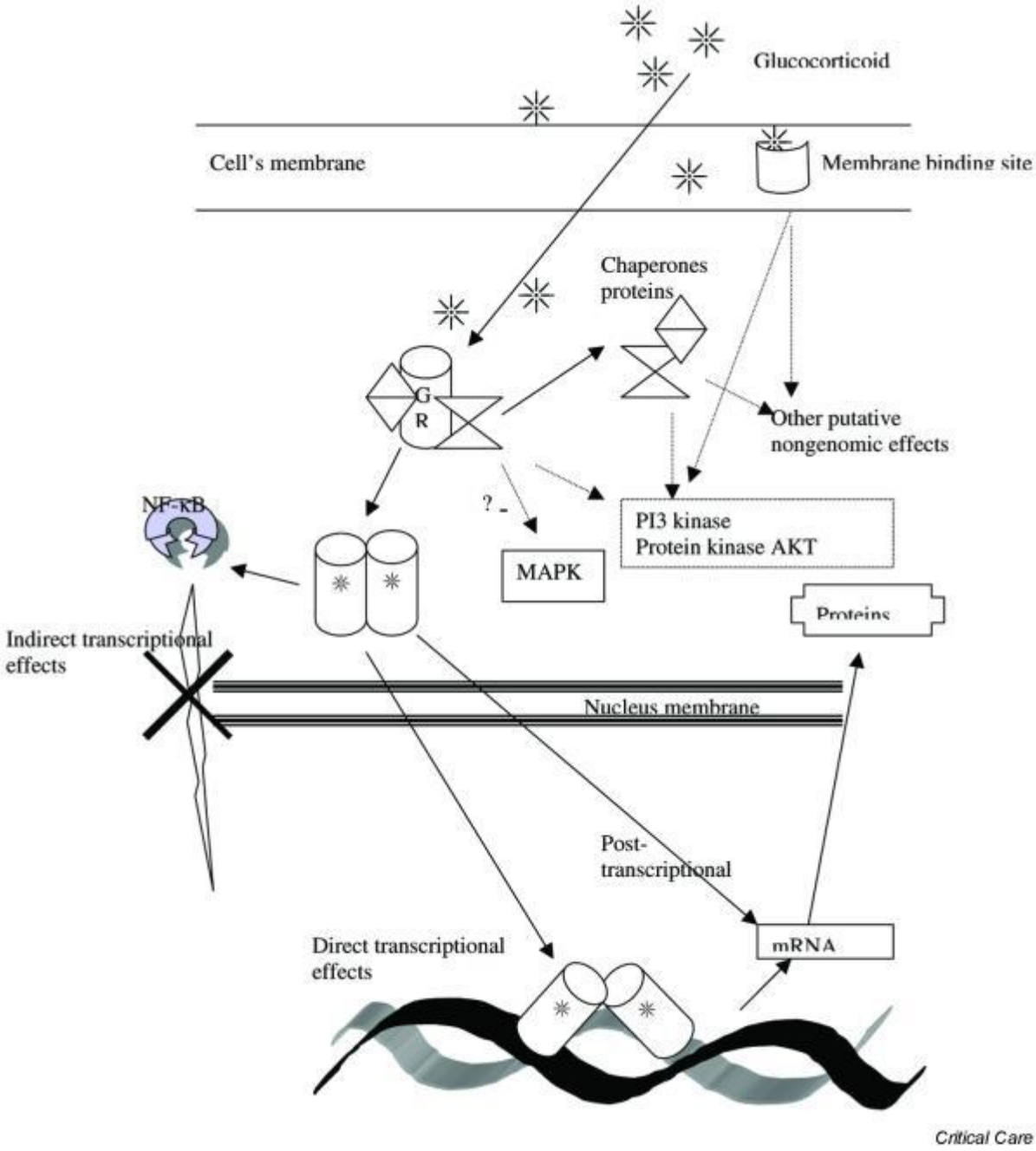

Figura 2. *Resumen de las acciones de los GC a nivel molecular desde el componente intersticial (Prignent, 2004).*

1.2. Efectos de los glucocorticoides en el paciente crítico

La enfermedad crítica en cualquiera de sus manifestaciones, representa un estrés de gran intensidad y persistente en el tiempo para los pacientes. De un modo general, el tratamiento debe encaminarse al reconocimiento del agente agresor y a la rápida restauración de los mecanismos fisiopatológicos afectados, con especial atención al sistema cardiovascular (Messotten, 2008). En los pacientes críticos, difícilmente puede alcanzarse un estado "eucorticoideo", que podría definirse como aquel en que la cantidad de cortisol endógeno secretado o el cortisol exógeno administrado se adapta a las necesidades del estrés (Burchard, 2001). Es bien conocido que los efectos de los corticoides sobre el sistema cardiovascular, metabólico e inmune representan un papel fundamental en la respuesta de adaptación al estrés.

Su influencia sobre el sistema cardiovascular ha recibido gran atención en la literatura. Los GC son necesarios para conseguir una correcta respuesta a la angiotensina II, adrenalina y noradrenalina, facilitando el mantenimiento de la contractilidad cardiaca, el tono vascular y la presión arterial (Cooper, 2003; Marik, 2002). Dichos efectos están mediados, en parte, por una elevada transcripción y expresión de los receptores de dichas hormonas y por un aumento de la sensibilidad contráctil a la noradrenalina (Sakaue, 1991; Annane, 1998). Además, los GC disminuyen la producción de óxido nítrico y prostaglandinas vasodilatadoras, relajantes vasculares y moduladores de la permeabilidad vascular, a través del bloqueo de la transcripción (Satoh, 2001; Matsumura, 2001).

Por otra parte, los GC aumentan la concentración de glucosa, facilitando su liberación a la circulación durante el estrés. Dicho efecto se consigue a través de un aumento de la gluconeogénesis hepática al aumentar la actividad de la glucosa-6-fosfatasa y una disminución de la recaptación por el tejido adiposo periférico (Pilkis, 1992). Otros mecanismos implicados incluyen una activación de la proteolisis y la liberación de ácidos grasos desde el tejido adiposo y la liberación de aminoácidos desde las proteínas. Todo ello representa un suplemento de energía a la célula en situaciones de estrés (Mesotten, 2008).

Finalmente, los GC poseen efectos antiinflamatorios e inmunosupresores que se encuentran mediados por diferentes mecanismos, fundamentalmente a través de la modulación del complejo de las citoquinas, factor de necrosis tumoral-α, activación del complemento y la inhibición del factor nuclear NF-kβ (Venkataraman, 2007; Mesotten, 2008).

Ante una situación de estrés, el organismo intenta elevar los niveles de cortisol como respuesta. Ésta se produce a través de diversos mecanismos, que pueden hallarse alterados en el enfermo crítico (Beishuizen, 2001; de Jong, 2006, Marsé Milla, 2008):

-Aumento la actividad GC a expensas de una disminución de la actividad mineralocorticoide.

-Aumento de la actividad de la CRH y la ACTH y disminución de los mecanismos de retroalimentación negativa.

-Aumento del número de RGC.

-Disminución de los niveles de GTC, con aumento de la fracción libre biológicamente activa.

- Modulación de las citoquinas pro/antinflamatorias, que pueden modificar el metabolismo del cortisol, inhibir la liberación de CRH y ACTH y reducir la afinidad del cortisol por los RGC.

1.3. Conceptos históricos y terminología

El estudio del eje HHS y el tratamiento con corticoides ha sido un tema de recurrente interés científico en las últimas décadas. La terminología utilizada para describir la afectación del eje HHS en los pacientes críticos ha ido evolucionando, incluyendo diferentes términos como insuficiencia suprarrenal, insuficiencia suprarrenal primaria, secundaria etc. Desde los trabajos de Annane emergió el concepto de insuficiencia suprarrenal relativa (ISR), ampliamente empleado en los estudios posteriores al año 2002 y que describe un incremento de las cifras de cortisol respecto al basal tras la estimulación glandular con 250 µg de ACTH sintética (también llamado high-dose corticotropin stimulation test (HDCST)) ≤ 9 µg/dL a los 30 y 60 minutos (Annane, 2000; Annane, 2002). Sin embargo, esta definición resulta controvertida, debido a que no se considera válida en pacientes con hipoalbuminemia (Hamrahian, 2004), no tiene en cuenta las cifras de cortisol basal (Venkataraman, 2007; Mesotten, 2008), existe un gran variabilidad entre los distintos sistemas de medición (Briegel, 2009) y no valora la gravedad de la enfermedad subyacente (Mesotten, 2008)

Por todo, ello, recientemente se ha acuñado el concepto de CIRCI (Critical Illness-Related Corticosteroid Insufficiency), que se define como la inadecuada respuesta del cortisol para la gravedad de la enfermedad subyacente (Marik, 2008; Marik, 2009), sin especificar consideraciones del diagnóstico bioquímico del fallo del eje HHS. Sin embargo, este término no se ha utilizado en la mayoría de estudios publicados hasta la fecha en la valoración del fallo del eje HHS en los pacientes críticos.

1.4. Diagnóstico del fallo del eje HHS

Diferentes cifras de cortisol basal, pico máximo tras estimulación, incremento de cortisol respecto al basal tras la estimulación glandular o combinaciones de los anteriores parámetros, se han propuesto como sugestivas de fallo del eje HHS (fundamentalmente bajo el término ISR). Como ya se ha señalado previamente, existen importantes dificultades técnicas en la determinación bioquímica de esta entidad (Arafah, 2006), que además se agravan si consideramos que en el paciente crítico el ritmo circadiano habitual en la secreción de cortisol se encuentra abolido en la mayor parte de los casos (Paul, 2007). Se detallan algunos de los parámetros empleados, sobre todo en los pacientes sépticos.

Cortisol basal

Un cortisol basal inferior a 10 µg/dL sería indicativo de ISR, mientras un cortisol basal por encima de 34 µg/dL permitiría excluir de forma razonable este diagnóstico (Lamberts, 1997). Marik y Zaloga realizaron un estudio con 59 pacientes en shock séptico, observando que una cifra de cortisol basal de 23,7 µg/dL era el valor más adecuado para el diagnóstico de ISR al predecir con mayor seguridad la repuesta hemodinámica al tratamiento con corticoides. Hallaron, con este criterio, una incidencia del ISR del 61% en pacientes con shock séptico (Marik, 2003). Sin embargo, otros autores encontraron una acusada variabilidad en determinaciones horarias de cortisol en enfermos sépticos (Venkatesh, 2005).

Incremento de cortisol tras estimulación de la glándula suprarrenal

Desde el estudio de Annane y cols (Annane, 2002), la estimulación de la glándula suprarrenal con 250 µg de ACTH sintética se ha convertido en el método de diagnóstico utilizado habitualmente en la mayoría de UCIs. Un incremento ≤ 9 µg/dL identificaría a los enfermos con ISR. Sin embargo, este método ha sido criticado, puesto que supone una estimulación suprafisiológica de la glándula suprarrenal (Marik, 2002; Widmer, 2005). De este modo, recientemente se ha propuesto el uso de 1 µg de ACTH sintética como método de elección en pacientes sépticos (Siraux, 2005) y traumáticos (Dimopoulou, 2004). Al tratarse de una dosis más fisiológica, seleccionaría un subgrupo de pacientes con ISR que el test con dosis altas no identificaría (Dimopoulou, 2004). Sin embargo, su uso en la valoración de ISR en el paciente crítico ha sido también criticado, puesto que dicha dosis podría no evaluar la máxima capacidad secretora de la glándula y además debe realizarse una dilución adecuada para obtener dicha dosis (Annane, 2005).

Pico de cortisol tras la estimulación suprarrenal

Otros autores consideran el pico de cortisol tras la estimulación suprarrenal como el mejor parámetro predictivo de la función de la glándula suprarrenal. Han sido propuestos valores de 18 µg/dL (Bouachaour, 1995; Soni, 1995) a 22 µg/dL (Patel, 1991). Hay que destacar que en un estudio retrospectivo que incluía 113 pacientes traumáticos con inestabilidad hemodinámica a los que se les estudió la función suprarrenal en los 10 primeros días tras el traumatismo, la respuesta a los 60 minutos tras el HDCST se correlacionó mejor con la máxima capacidad secretora de la glándula (Bernard, 2006).

Cortisol basal y estimulado

Se han propuesto diferentes algoritmos que combinan los valores de cortisol basal y la respuesta a la estimulación glandular para el diagnóstico de ISR (Annane, 2003, Gonzalez, 2006, ver Figura 3). Este enfoque lleva al concepto de resistencia tisular a los GC, que reflejaría una situación en la que se produce una disminución de la actividad GC, al interactuar el sistema inmune sobre la síntesis de GTC, y secundariamente, sobre la liberación de cortisol en el hígado. Debería sospecharse ante la presencia de un cortisol basal superior a 34 µg/dL con una respuesta al HDCST superior a 9 µg/dL (Annane, 2003).

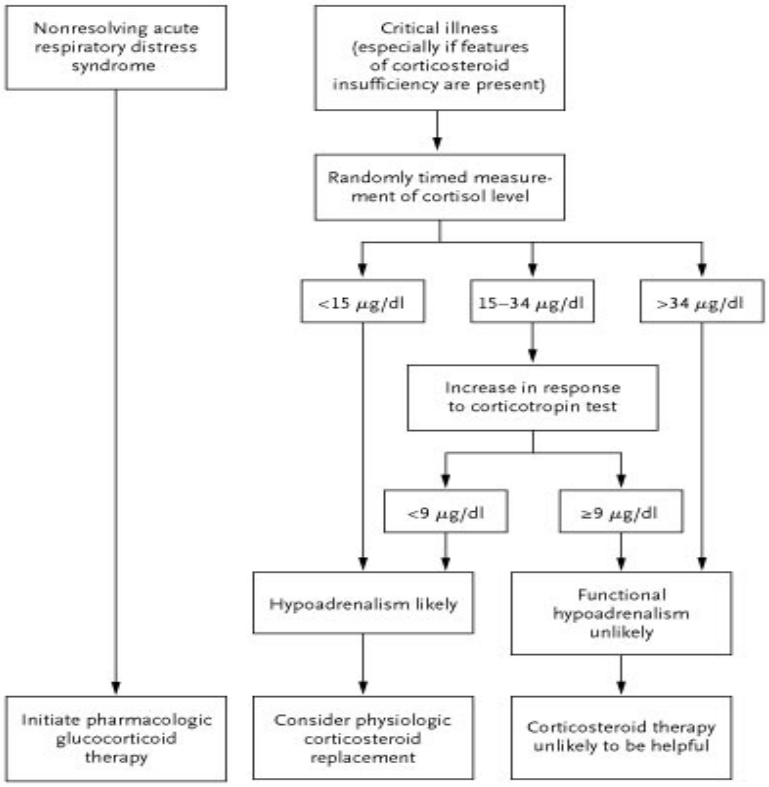

***Figura 3**. Algoritmo recomendado que incluye la determinación de cortisol basal y tras HDCST en pacientes críticos (Cooper, 2003).*

Determinación de cortisol libre

Algunos autores han propuesto el uso de la determinación de cortisol libre (porción biológicamente activa), que refleja de un modo más preciso la función del eje HHS en pacientes críticos (Hamrahian, 2005; Ho, 2006). Sin embargo, la experiencia es limitada y la determinación de cortisol libre no se encuentra disponible en la mayoría de centros.

1.5. Relación entre la función del eje HHS y la mortalidad

La incidencia de ISR o CIRCI en el paciente crítico es variable según cuales sean los criterios diagnósticos utilizados (Marik, 2002; Arafah, 2006; Bernard, 2006; de Jong, 2006; Marsé Milla, 2008).

Tanto la determinación de cortisol basal, como la determinación del pico de cortisol tras la estimulación glandular, el incremento de cortisol tras la estimulación glandular y una combinación de cortisol basal y tras estimulación han sido evaluados (Ligtenberg, 2004; Bollaert, 2003; Bernard, 2006, Marsé Milla, 2008). Los valores asociados con la mortalidad han sido discordantes, aunque, en general, unos niveles elevados de cortisol basal y un incremento ≤ 9 µg/dL tras la estimulación glandular con 250 µg de ACTH sintética son los valores más consistentemente asociados a un incremento de la mortalidad, especialmente en pacientes sépticos (Lamberts, 1997; Annane, 2000; Bollaert, 2003; De Jong, 2006). El estudio más ambicioso en términos pronósticos fue el publicado por Annane y cols (Annane, 2000). En dicho estudio, incluyendo 189 pacientes críticos se establecieron los siguientes grupos con diferente supervivencia asociada:

-Cortisol basal < 34 µg/dL e incremento del cortisol tras la estimulación glandular con 250 µg de ACTH sintética ≤ 9 µg/dL: supervivencia del 18%

-Cortisol basal > 34 µg/dL e incremento de cortisol tras estimulación > 9 µg/dL o cortisol basal < 34 µg/dL e incremento de cortisol ≤ 9 µg/dL: supervivencia del 32%.

-Cortisol basal < 34 µg/dL e incremento de cortisol > 9 µg/dL: supervivencia del 70%.

1.6. Manifestaciones clínicas de la disfunción del eje HHS

Las manifestaciones clínicas sugestivas de CIRCI en el paciente crítico son a menudo inespecíficas, o difícilmente valorables en un paciente conectado a ventilación mecánica, inestable hemodinámicamente, sedado y con múltiples factores de confusión. Los pacientes con un trastorno crónico del eje HHS pueden presentar síntomas como debilidad, pérdida de peso, anorexia, letargia y en algunos casos náuseas, vómitos, dolor abdominal y diarrea. Los análisis pueden mostrar hiponatremia, hiperpotasemia, hipoglucemia y anemia normocítica. En el caso del CIRCI, las manifestaciones clínicas son consecuencia de una exagerada respuesta proinflamatoria, y la hipotensión arterial refractaria a fluídos es su manifestación más frecuente y relevante clínicamente. El laboratorio puede mostrar eosinofilia e hipoglucemia, aunque éstos no sean datos con gran especificidad (Cooper, 2003; Marik, 2003, Marik, 2009).

1.7. Papel del tratamiento sustitutivo con corticoides

Debido a la repercusión clínica de la hipotensión refractaria a volemia, manifestación fundamental del CIRCI, es entendible el interés en el estudio del eje HHS en los pacientes críticos ingresados en la Unidad de Cuidados Intensivos (UCI). De entre los pacientes críticos, destacan los estudios realizados en dos poblaciones: los pacientes con sepsis severa/shock séptico y los pacientes con traumatismo craneoencefálico (TCE).

1.7.1. Sepsis

Los pacientes sépticos habitualmente presentan una vasodilatación profunda con una circulación hiperdinámica, que se puede modificar en el curso de la sepsis. En este contexto, se produce una hipotensión arterial severa, con un cuadro establecido de shock séptico, que presenta tasas de mortalidad en torno al 50%. Los esfuerzos terapéuticos, se centran, entre otras medidas, en una rápida restauración hemodinámica, y en este contexto, es donde puede jugar un papel importante la existencia de CIRCI y el potencial tratamiento sustitutivo con corticoterapia.

Como ya se ha reseñado previamente el diagnóstico bioquímico de la entidad es complejo por cuestiones metodológicas. Sin embargo, el tratamiento con corticoides (fundamentalmente por sus efectos cardiovasculares, pero también inmunológicos) se ha estudiado desde hace varias décadas.

El uso de dosis altas de corticoides en pacientes sépticos se ha evaluado desde los años 80. Algunos estudios mostraron su falta de eficacia, con un marcado aumento en el número de complicaciones asociadas (Sprung, 1984; Luce, 1988). Este hecho llevó al abandono de este tratamiento, hasta que los estudios preliminares del grupo de Annane sugirieron un papel importante de la disfunción HHS en estos pacientes (Annane, 2000). En la última década, se ha retomado el estudio del tratamiento con corticoides, en esta ocasión con dosis menores (fisiológicas) de hidrocortisona con/sin fludrocortisona. Este tratamiento se ha llamado tratamiento sustitutivo suprarrenal o “low-dose steroid therapy (LDST)”. El estudio de Annane y cols (Annane, 2002), incluyó 299 pacientes en shock séptico a los que se les realizó una prueba de

estimulación suprarrenal con 250 µg de ACTH sintética y fueron tratados con hidrocortisona 50 mg/6horas iv. asociada a fludrocortisona 50 µg/24h por vía digestiva frente a placebo. Un total de 229 pacientes (76%) incrementaron la cifra de cortisol tras la estimulación ≤ 9 µg/dL, considerándose respuesta anormal. En este subgrupo (predefinido) la mortalidad a los 28 días fue inferior en el grupo tratado con corticoides respecto a placebo (53% frente a 63%; p = 0,02), y se pudo retirar de modo más precoz el soporte vasoactivo. Sin embargo, en el grupo de pacientes con respuesta normal (incremento superior a 9 µg/dL), se observó una tendencia (no significativa) a una mayor mortalidad entre los pacientes tratados con LDST. La incidencia de efectos adversos secundarios fue la misma en los pacientes tratados con corticoides que con placebo. Además del estudio de Annane y cols, diversos trabajos han mostrado una disminución en las necesidades de noradrenalina y un menor tiempo hasta su retirada en series reducidas de pacientes en shock séptico tratados con LDST (Bollaert, 1998; Briegel, 1999; Oppert, 2000; Marik, 2003; Keh, 2003), existiendo cierto consenso en los beneficios hemodinámicos en cuanto a la reducción del tiempo de shock (Annane, 2009; Sligl 2009).

Sin embargo, y ante las críticas metodológicas recibidas por los estudios previos (Ligtenberg, 2004; Keh, 2004, Thys, 2005), se llevó a cabo un estudio europeo multicéntrico (CORTICUS), en buena parte realizado por los mismos autores, que debía determinar el papel definitivo de la terapia sustitutiva suprarrenal en pacientes sépticos (Sprung, 2008). Lejos de confirmar los resultados del estudio de Annane y cols, el estudio CORTICUS mostró que el uso de hidrocortisona (50 mg/6h iv. y desescalonamiento progresivo a partir del 6º día) en el shock séptico no se asoció a una disminución de la mortalidad,

aunque sí a una reducción del tiempo de shock en una población de 499 pacientes. Además evidenció el limitado papel de la estimulación glandular con HDCST como guía del tratamiento con corticoides en estos pacientes. Sin embargo, este estudio también tiene limitaciones, entre las que destacan un bajo poder estadístico al no reclutarse los 800 pacientes previstos, la inclusión de pacientes con menor gravedad definida por índices de gravedad e incidencia de hipotensión arterial, el predominio de pacientes quirúrgicos y el uso de hidrocortisona sin fludrocortisona y con desescalonamiento progresivo del tratamiento. Debido a estos aspectos, los estudios de Annane y Sprung no son equiparables en su totalidad.

En cualquier caso, los resultados del este estudio han llevado a modificar el grado de recomendación de dicho tratamiento en las guías de la *Surviving Sepsis Campaign*, que recomienda el uso de corticoides sólo en aquellos casos con disfunción orgánica e hipotensión arterial refractaria a la reposición de volemia y fármacos vasoactivos (Dellinger, 2008). La controversia existente en los pacientes sépticos respecto al papel de la terapia sustitutiva suprarrenal y su influencia sobre la mortalidad se refleja en las diferentes interpretaciones de los 2 metaanálisis más recientes (Annane, 2009; Sligl, 2009).

El primer trabajo (Annane, 2009), incluyendo todos los estudios aleatorizados realizados con cualquier tipo de corticoide y a diferentes dosis en pacientes con shock séptico muestra una disminución de la mortalidad en los pacientes tratados (ver Figura 4). El segundo trabajo (Sligl, 2009), que incluye los estudios aleatorizados recientes en los que se empleó la LDST y los dos estudios retrospectivos con mayor peso estadístico en pacientes sépticos, concluyó que el tratamiento con LDST no se asoció a una disminución de la

mortalidad en la población global ni en los grupos de pacientes con buena o mala respuesta a la estimulación glandular suprarrenal (ver Figura 5).

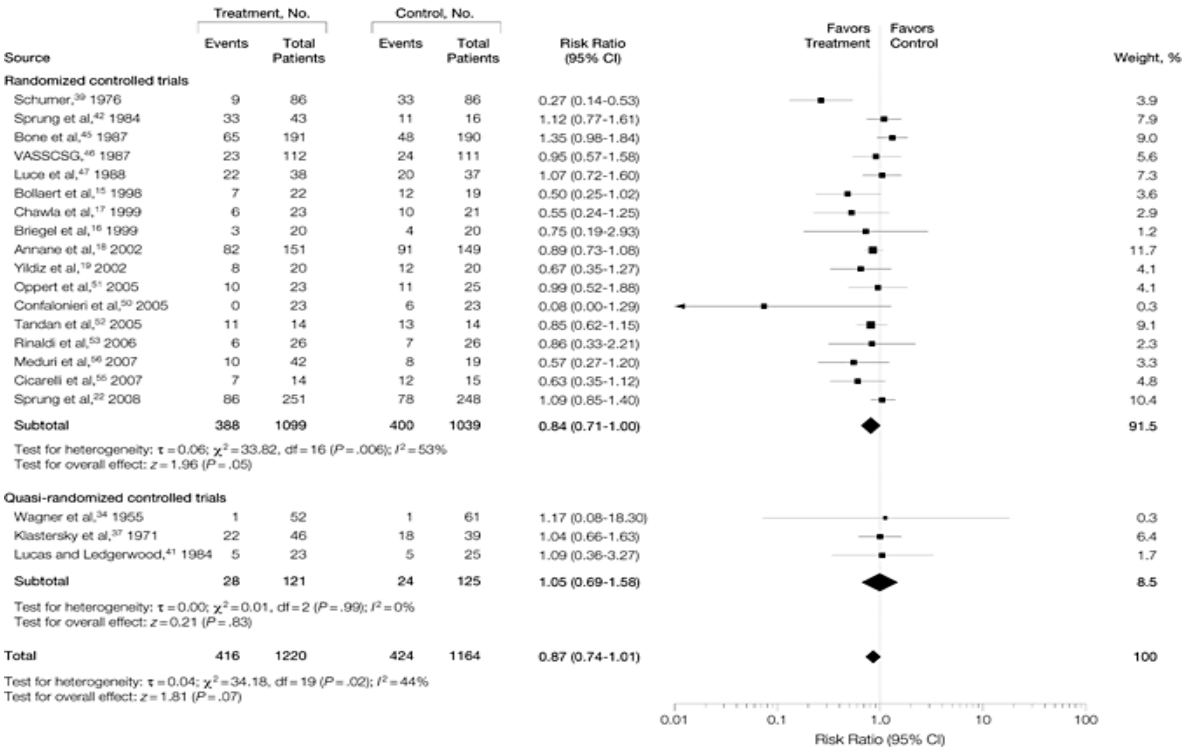

Figura 4. *Mortalidad a los 28 días según tratamiento con corticoides o placebo en el shock séptico (Annane, 2009).*

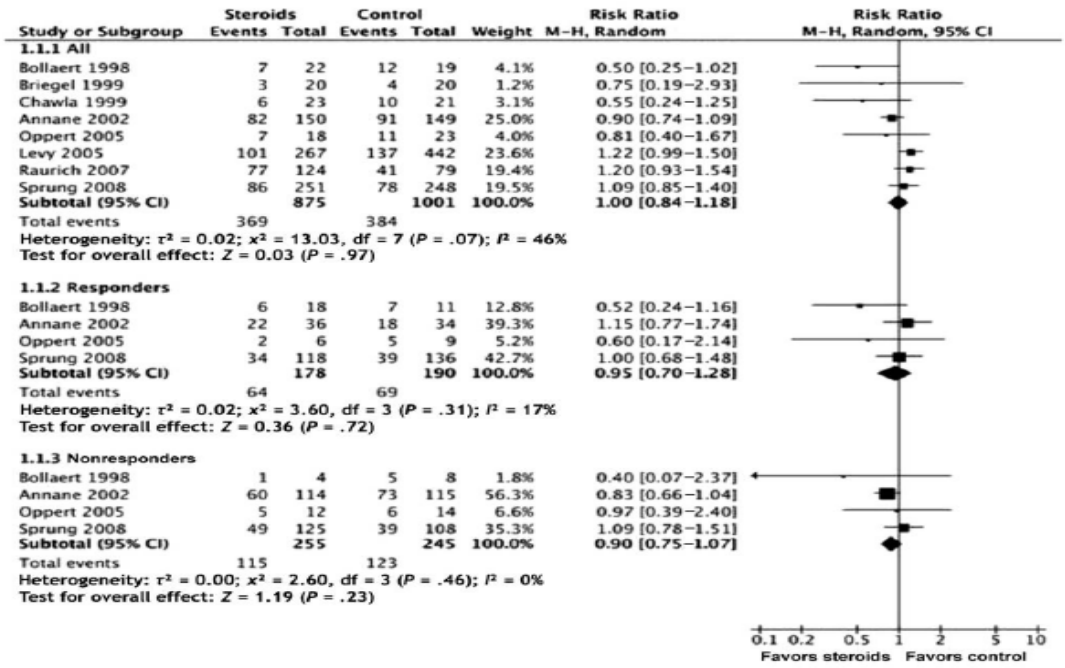

Figura 5. *Mortalidad a los 28 días según tratamiento con corticoides o placebo en el shock séptico (Sligl, 2009).*

1.7.2. Traumatismo craneoencefálico

La función del eje HHS en el paciente con TCE presenta unas características especiales que deben ser consideradas. Los pacientes con TCE presentan en muchas ocasiones un traumatismo directo sobre el área hipotalámica e hipofisaria, cuya vascularización y características anatómicas hacen que sea especialmente sensible a las agresiones traumáticas (Koiv, 1997; Dimopoulou, 2005, ver Figura 6).

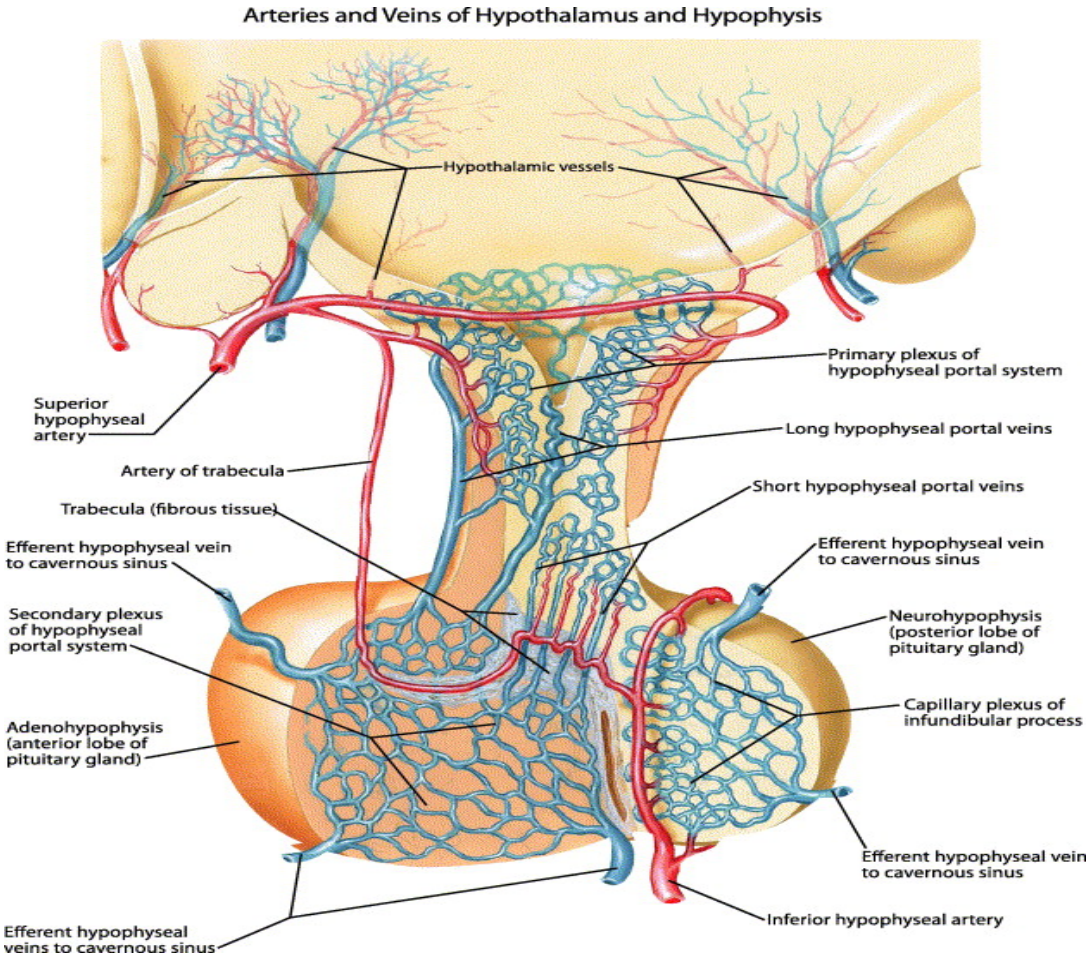

***Figura 6**. Vascularización y anatomía del área hipotálamico-hipofisaria (Urban, 2006).*

La agresión traumática puede resultar tanto en una estimulación como en una inhibición de la función hipofisaria y la respuesta suprarrenal (Koiv, 1997). Recientes estudios con resonancia magnética cerebral han mostrado diversas lesiones mediadas por el propio TCE y por fenómenos de necrosis celular, siendo más frecuente hallarlas en aquellos pacientes con TCE que también presentan alteraciones endocrinas (Schneider, 2007). Todo ello hace que sea difícil establecer a qué nivel se produce la disfunción del eje HHS en estos pacientes. Mientras algunos autores afirman que en la mayor parte de las ocasiones la disfunción del eje se produce a nivel glandular (afectación primaria) (Dimopoulou, 2004; Dimopoulou, 2005), otros autores sugieren que la afectación puede producirse también a nivel hipotalámico e hipofisario (afectación secundaria) (Cohan, 2005; Bernard, 2006). Además, hay que señalar que la hipotensión arterial severa es una complicación frecuente en los pacientes con TCE, principalmente cuando concurren otras lesiones y la necesidad de emplear algunos tratamientos. Dicha hipotensión arterial se asocia de modo significativo a un peor resultado neurológico final debido al aumento de la lesión cerebral secundaria (Brain Trauma Foundation, 2007, ver Figura 7).

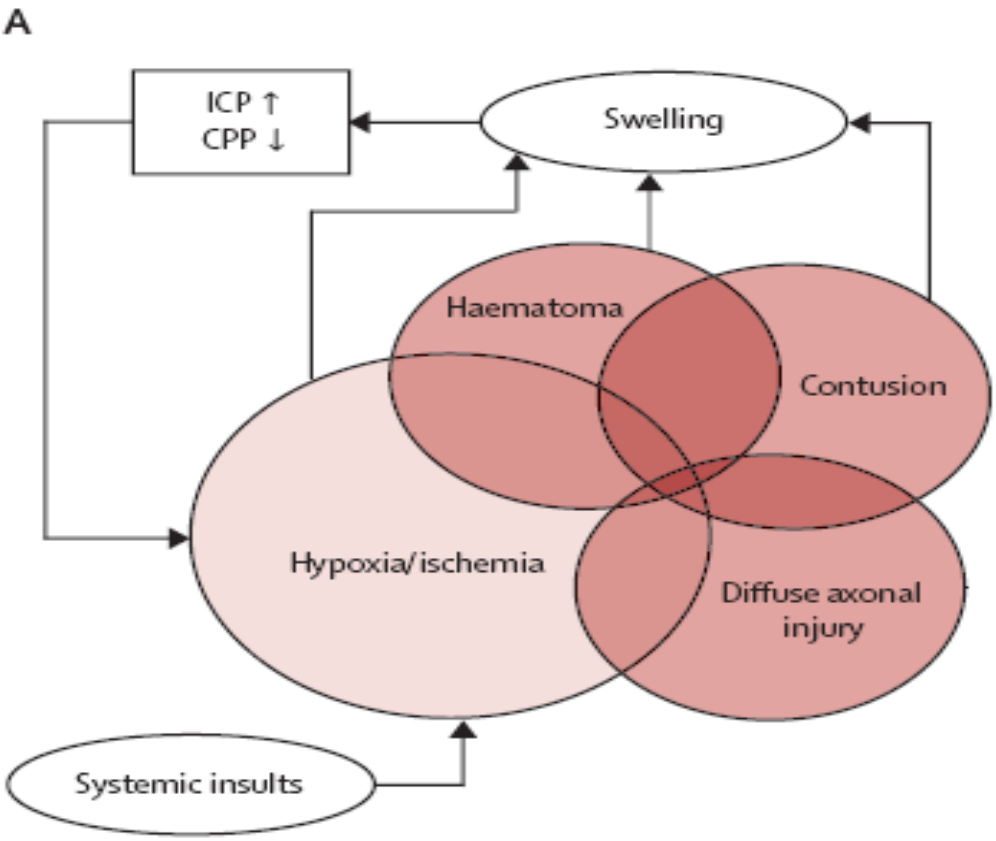

***Figura 7**. Mecanismos implicados en la lesión cerebral secundaria (Maas, 2008).*

Esta hipotensión puede estar mediada por la disfunción del eje HHS, por lo que teóricamente, estos pacientes podrían beneficiarse del tratamiento con LDST, al igual que puede ocurrir en los pacientes sépticos. Es conocido que los corticoides, a través de diversos mecanismos, incrementan la respuesta a la angiotensina II, adrenalina y noradrenalina, facilitando el mantenimiento de la contractilidad cardíaca, el tono vascular y la presión arterial (Annane, 1998). Algunos autores han sugerido que aquellos pacientes con TCE e inestabilidad hemodinámica en los que se detectara una disfunción suprarrenal, podrían beneficiarse del tratamiento con LDST, con intención de reducir los episodios

de hipotensión arterial y la isquemia secundaria en la fase aguda del TCE (Hoen, 2002; Dimopoulou, 2004; Cohan, 2005; Bernard, 2006).

En cuanto a la interrelación entre la función del eje HHS y el TCE, dos estudios son reseñables. Uno de ellos, realizado por nuestro grupo (Llompart-Pou, 2007, ***Anexo 1***) mostró que los pacientes con TCE que precisaban coma barbitúrico para el control de la hipertensión intracraneal presentaban mayor incidencia de hipotensión arterial. En el grupo tratado con barbitúricos, aquellos que presentaron hipotensión arterial severa (la mayor limitación de dicho tratamiento) presentaban afectación del eje HHS con mayor frecuencia, y ello se asoció a unos requerimientos de soporte vasoactivo mucho mayores, identificando un subgrupo de pacientes en los que el tratamiento sustitutivo suprarrenal podría resultar especialmente beneficioso. Sólo un estudio, de modo retrospectivo y con un número muy reducido de pacientes ha analizado el efecto del tratamiento sustitutivo con LDST en pacientes con TCE (Bernard, 2006), y mostró que los pacientes con buena respuesta hemodinámica a los corticoides presentaron un mejor pronóstico. Considerando esta limitada experiencia y conociendo que el mayor estudio realizado con corticoides (con otro GC y a dosis mucho más elevadas) en 10008 pacientes con TCE, demostró que los pacientes tratados presentaron una mayor mortalidad y un peor resultado neurológico funcional final (Edwards, 2005), la utilidad del tratamiento con LDST para la insuficiencia suprarrenal postraumática debe ser evaluada en un ensayo clínico adecuado. Además, debe tenerse en consideración la amplia variabilidad en la incidencia de disfunción del eje HHS

en función de la definición empleada (Bernard, 2006), que oscilaría desde un 13% al 100% (ver Figura 8).

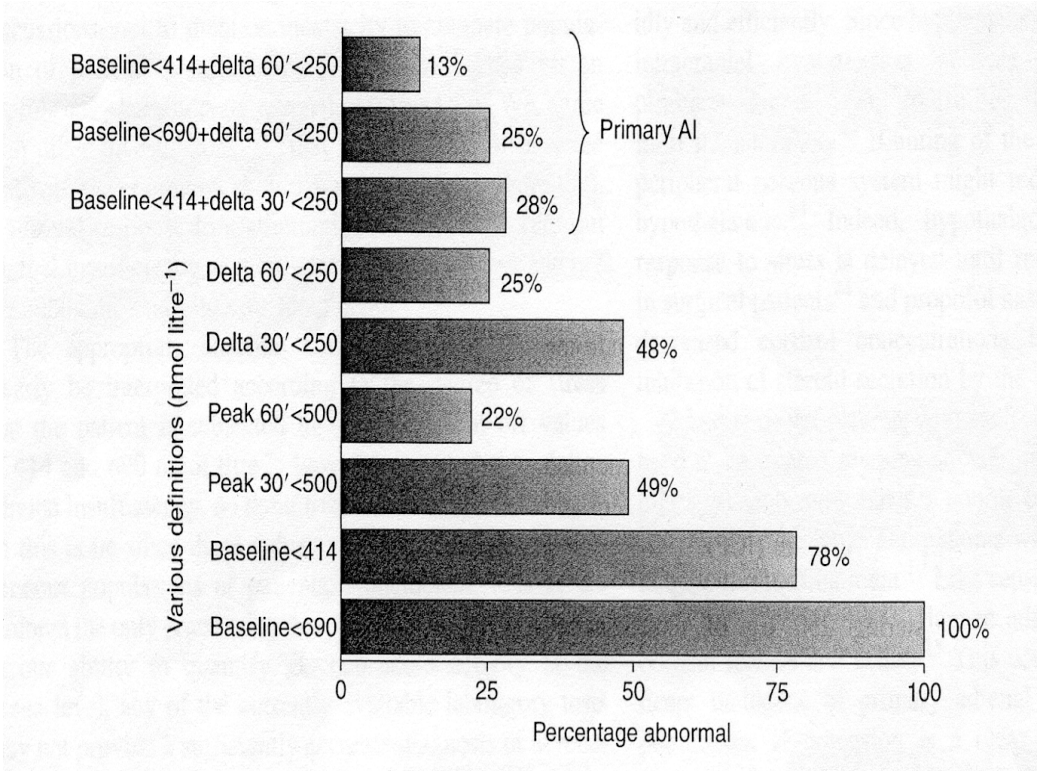

***Figura 8**. Incidencia de ISR según la definición empleada (Bernard, 2006).*

Por ello, pensamos que previo a cualquier estudio evaluando el tratamiento sustitutivo con corticoides en pacientes con TCE, debe caracterizarse adecuadamente la respuesta del eje HHS en la fase aguda del TCE y su potencial influencia en el resultado final de estos pacientes.

2. Justificación, hipótesis y objetivos de trabajo

2.1. Justificación

Aún considerando la extensa bibliografía aparecida en los últimos 10 años, el estudio de la disfunción HHS en el paciente crítico continúa siendo un área de debate. Por todo ello creemos necesario profundizar en nuevos estudios, tanto en el ámbito clínico como en el experimental, con las nuevas técnicas disponibles en la UCI.

Por ello este trabajo se inició con el estudio de la función del eje HHS y el papel del tratamiento con LDST en una población de pacientes con shock séptico no seleccionados, evaluando la correlación hemodinámica con las cifras de cortisol basal y tras estimulación con ACTH sintética.

La segunda parte de esta tesis continúa con el estudio del eje HHS en pacientes con TCE, que como se ha dicho presentan características especiales, estableciendo la incidencia de disfunción del eje HHS, los factores de riesgo asociados y su relación con el pronóstico de estos pacientes.

Puesto que los estudios clínicos en los pacientes críticos han mostrado resultados dispares, creemos que el estudio del eje HHS debe encaminarse hacia aspectos más novedosos, como la determinación de la concentración de cortisol en el espacio intersticial. Así, en la tercera parte de este trabajo se presenta nuestra experiencia en la evaluación de las cifras de cortisol en el intersticio cerebral en pacientes con TCE, un aspecto nunca desarrollado previamente.

2.2. Hipótesis de trabajo

El estudio completo del eje HHS en el paciente crítico y su relación con la respuesta ante el estrés y el papel del tratamiento sustitutivo con corticoides puede jugar un papel relevante en estos pacientes, así como la investigación de nuevos modos de estudio de la disponibilidad de cortisol tisular.

2.3. Objetivos

1) Evaluar la respuesta hemodinámica al tratamiento con corticoides en pacientes sépticos y su correlación con las cifras de cortisol basal y tras estimulación glandular.

2) Determinar el patrón de respuesta HHS en el paciente con TCE, los factores de riesgo asociados y su relación con el pronóstico y resultado final.

3) Investigar la disponibilidad de cortisol en el intersticio cerebral en pacientes con TCE y si ésta presenta un ritmo biológico preservado.

3. Pacientes y métodos

Todos los pacientes estudiados se encontraban ingresados en la UCI del Hospital Universitario Son Dureta. En todos los casos, los estudios fueron aprobados por la comisión de investigación del Hospital Universitari Son Dureta, y en los estudios con microdiálisis cerebral por el Comité Ètic de les Illes Balears.

El manejo de los mismos se realizó de acuerdo a las guías internacionales de tratamiento, para los pacientes con las dos patologías fundamentales estudiadas: Shock séptico (Dellinger, 2008) y TCE (Bullock, 1996).

El manejo de los pacientes sépticos se encamina a un rápido reconocimiento del foco infeccioso y tratamiento antibiótico dirigido, aporte de volemia adecuada y restauración hemodinámica precoz con soporte vasoactivo si es necesario, tratamiento con corticoides y proteína C activada si se encuentra indicado y control de factores sistémicos (por ejemplo, la glucemia) con potencial influencia sobre la homeostasis (Dellinger, 2008).

En los pacientes con TCE que cursan con hipertensión intracraneal, el objetivo fundamental es el control de la presión intracraneal por debajo de 20 mmHg, con una presión de perfusión cerebral superior a 60 mmHg y evitando siempre los insultos sistémicos que influyen de modo marcado en el pronóstico de estos pacientes. La hipertensión intracraneal se trata siguiendo un algoritmo secuencial que incluye medidas generales (sedación, optimización hemodinámica y respiratoria), medidas de primer nivel (osmoterapia, drenaje de líquido cefalorraquídeo a través de drenaje ventricular) y medidas de segundo nivel cuando la hipertensión intracraneal se hace refractaria (coma barbitúrico, hipotermia moderada, craneotomía descompresiva o colocación de drenaje lumbar) (Bullock, 1996).

La explicación detallada de los procedimientos estadísticos realizados se describe en el apartado de metodología de los 6 artículos publicados.

3.1. Estudios en pacientes sépticos

En el primer estudio (***Journal Critical Care, 2007***) se evaluaron de modo retrospectivo 203 pacientes con shock séptico ingresados en la UCI de nuestro hospital en los que se había realizado un test de estimulación glandular con 250 µg de ACTH sintética. Los pacientes fueron tratados de acuerdo a las recomendaciones internacionales y la decisión de realizar o no tratamiento sustitutivo suprarrenal tras la estimulación glandular se tomó por parte del médico intensivista responsable del paciente. Se comparó la respuesta hemodinámica en 124 pacientes que recibieron tratamiento con corticoides y 79 pacientes que no recibieron dicho tratamiento. Para ajustar ambos grupos por factores de confusión, empleamos el análisis estadístico *propensity score* (Joffe, 1999). El objetivo fundamental del estudio fue evaluar la influencia del tratamiento con corticoides en la mortalidad y tiempo de shock de estos pacientes.

En el segundo estudio en pacientes sépticos (***Medicina Intensiva, 2008***), se estudiaron de modo retrospectivo 96 pacientes con shock séptico. Un total de 48 fueron tratados con terapia sustitutiva suprarrenal y el grupo control se compuso por otros 48 pacientes que no recibieron dicho tratamiento, apareados ambos grupos de acuerdo a intervalos de cortisol basal de 5 µg/dl y dosis de Noradrenalina en diferencias inferiores al 20%. El objetivo fundamental del estudio fue evaluar la variación en la dosis de Noradrenalina a las 24 horas de haber recibido o no LDST.

3.2. Estudios en pacientes con TCE

En el primer estudio de pacientes con TCE (***Journal Trauma, 2007***) evaluamos de modo prospectivo 50 pacientes con TCE aislado, que recibieron sedación, ventilación mecánica y monitorización de la presión intracraneal ingresados consecutivamente en la UCI de nuestro hospital. En las primeras 48 horas de ingreso se realizó el HDCST, obteniendo muestras para ACTH y cortisol basal y cortisol tras 30 y 60 minutos tras la estimulación. El objetivo fundamental del estudio fue correlacionar la respuesta del eje HHS con la mortalidad en los pacientes con TCE.

En el segundo estudio con pacientes con TCE (***Neurocritical Care, 2008***) estudiamos de modo prospectivo un total de 165 pacientes con TCE ingresados en nuestra unidad. En todos los casos se realizó un test de estimulación suprarrenal empleando HDCST, obteniendo muestras para ACTH y cortisol basal y cortisol tras 30 y 60 minutos tras la estimulación, entre las 08:00h y las 10:00h. El objetivo principal del estudio fue identificar la incidencia de disfunción HHS en la fase aguda del TCE, de acuerdo a definiciones previamente empleadas en pacientes traumáticas. Como objetivos secundarios evaluar la influencia del traumatismo extracraneal, sedantes y determinar los factores de riesgo asociados a la disfunción HHS.

3.3. Estudios con microdiálisis cerebral

La microdiálisis cerebral es una técnica semi-invasiva en la que se implanta un catéter provisto de una membrana semipermeable, que permite obtener diferentes solutos desde el intersticio cerebral (De los Ríos, 2009, ver Figura 9). Se emplea habitualmente para la evaluación del metabolismo cerebral (glucosa, lactato, piruvato, etc), pero también puede emplearse para medir otras sustancias, como las concentraciones de fármacos antibióticos (Caricato, 2006) o antiepilépticos (Tisdall, 2006; Rambeck, 2006). Recientemente ha sido empleada para determinar la disponibilidad de cortisol en el tejido lesionado en pacientes quemados, comparando tejido sano y tejido afectado por las quemaduras (Cohen, 2009).

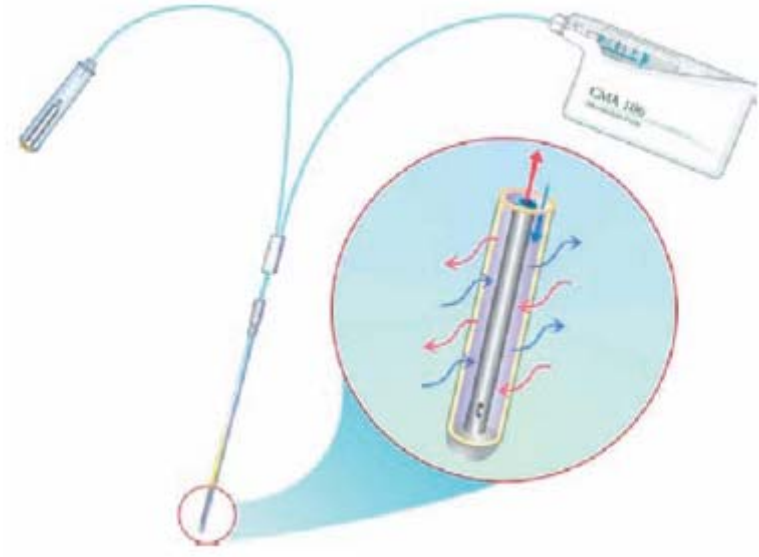

Figura 9: *Catéter de microdiálisis que muestra en su punta la membrana semipermeable donde se realiza el intercambio de solutos (De Los Ríos, 2009).*

En nuestro primer estudio preliminar ***(Journal Endocrinological* Investigation, 2010)** incluyendo 6 pacientes, se inyectó la sustancia de infusión a un ritmo de 0.3 µL/minuto. Los viales se recambiaron cada 8 horas. A la vez se obtuvieron muestras de suero que se congelaron hasta el análisis. El objetivo fundamental del estudio fue correlacionar los niveles de cortisol sérico total con los valores de cortisol en el microdializado, es decir, en el intersticio cerebral.

En el segundo estudio, incluyendo un total de 10 pacientes ***(Neurocritical Care, 2010)*** se evaluó la existencia o no de variabilidad de las cifras de cortisol sérico y cortisol tisular cerebral siguiendo un ritmo circadiano, siguiendo la misma metodología descrita en el estudio anterior.

4. Resultados

Listado de los artículos que forman parte de la tesis doctoral:

1. Low dose steroid therapy does not affect hemodynamic response in septic shock patients. Raurich JM, Llompart-Pou JA, Ibáñez J, Frontera G, Pérez O, García de Carlos L, Ayestarán JI. ***J Crit Care 2007; 22:324-9.***

2. Respuesta hemodinámica precoz a los corticoides en el shock séptico. Llompart-Pou JA, Raurich JM, Ibáñez J, Riesco M, Ayestarán JI. ***Med Intensiva 2008; 32:385-90.***

3. Relationship between plasma adrenocorticotropin hormone and intensive care unit survival in early traumatic brain injury. Llompart-Pou JA, Raurich JM, Ibáñez J, Burguera B, Ayestarán JI, Pérez-Bárcena J. ***J Trauma 2007; 62:1457-61***.

4. Acute HPA response in traumatic brain injury with and without extracerebral trauma. Llompart-Pou JA, Raurich JM, Pérez-Bárcena J, Barceló A, Ibáñez J, Ayestarán JI. ***Neurocrit Care 2008; 9:230-6***.

5. Correlation between brain interstitial and total serum cortisol levels in traumatic brain injury. A preliminary study. Llompart-Pou JA, Pérez G, Pérez-Bárcena J, Brell M, Ibáñez J, Riesco M, Abadal JM, Homar J, Marsé P, Ibáñez, Burguera B, Raurich JM. **J Endocrinol Invest 2010; 33:368-72.**

6. Loss of cortisol circadian rhythm in patients with traumatic brain injury: a microdialysis evaluation. Llompart-Pou JA, Pérez G, Raurich JM, Riesco M, Brell M, Ibáñez J, Pérez-Bárcena J, Abadal JM; Homar J, Burguera B. **Neurocrit Care 2010**.

Low dose steroid therapy does not affect hemodynamic response in septic shock patients. Raurich JM, Llompart-Pou JA, Ibáñez J, Frontera G, Pérez O, García de Carlos L, Ayestarán JI. ***J Crit Care 2007; 22:324-9.***

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Low-dose steroid therapy does not affect hemodynamic response in septic shock patients

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Keywords:
Low-dose steroid therapy;
Cortisol;
Shock reversal;
Mortality;
Septic shock;
Propensity score

Abstract

Purpose: Several studies showed that low-dose steroid therapy (LDST) in patients with septic shock leads to a significantly shorter duration of shock and a decreased mortality. However, these results have been criticized. Our purpose was to evaluate the effects of LDST on time to shock reversal and mortality in septic shock.

Materials and Methods: We retrospectively studied 203 patients with septic shock admitted to the intensive care unit of our tertiary hospital. A short corticotropin test was performed in all patients within 72 hours of septic shock onset. We performed a propensity score analysis through a logistic regression model with baseline relevant characteristics, and evaluated the influence of LDST on time to shock reversal and inhospital mortality.

Results: One hundred twenty-four patients were treated with LDST (steroid group) and 79 without LDST (control group). Patients treated with steroids presented higher Simplified Acute Physiology Score II and maximum Sepsis-Related Organ Failure Assessment scores. Both groups presented similar baseline and stimulated cortisol values. The hazard ratio of remaining on shock adjusted by severity of illness, inadequate antibiotic, and propensity score was 1.15 (95% confidence interval 0.71-1.86) for patients treated with steroids. Inhospital mortality was 62% in the steroid group and 52% in the control group (P = .84). Logistic regression analysis with propensity score neither showed differences between steroid and control group in the inhospital mortality. Predictors of inhospital mortality were age, maximum Sepsis-Related Organ Failure Assessment score, and inadequate antibiotics.

Conclusion: In our study, treatment with low-dose steroid therapy was not associated to a reduction in time to shock reversal or mortality.

1. Introduction

Despite recent advances in the therapy of septic shock [1], mortality is still too high [2]. One of the treatments in which attention has been focused in late years is the low-dose steroid therapy (LDST).

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Cortisol has been suggested to contribute to maintain cardiac contractility, vascular tone, and blood pressure by different mechanisms [3-6]. Annane et al [7] showed that septic shock patients with a blunted adrenal response (defined by an increase less than 9 μg/dL after stimulation of adrenal gland with high-dose corticotropin hormone) had a reduced time to shock reversal and a lower mortality if they were treated with hydrocortisone and fludrocortisone. Another small prospective studies also showed a hemodynamic benefit from LDST in septic shock [6,8,9]. Based on these studies, guidelines consider LDST use in septic shock patients with a grade C level of evidence [1]. However, controversy exists on several points. The most important is that there exists no consensus regarding the definition of adrenal insufficiency in critically ill patients, and incidence clearly varies depending on the definition used [3,11]. Due to these controversies, several authors support that septic shock patients who present with hemodynamic instability after adequate fluid resuscitation should be treated with steroids irrespective of the biochemical parameters [11-16].

The aim of this study was to evaluate if LDST reduces the time to shock reversal and its influence on inhospital mortality in septic shock patients.

2. Materials and methods

2.1. Patients

We retrospectively selected patients from a database including 203 patients with septic shock who had their adrenal function tested with the high-dose corticotropin stimulation test (HDCST) and were admitted to the intensive care unit (ICU) of our tertiary University Hospital (Hospital Universitario Son Dureta) from April 2001 to November 2005. During the study period, 289 patients met the inclusion criteria (70% included). We did not include patients who had previously received drugs known to interfere with cortisol secretion (steroids, etomidate, ketoconazole). Hospital Research Committees approved the study and waived the need of informed consent because it was an observational and retrospective study.

Patients enrolled met these criteria: the presence of septic shock including proven or strongly suspected infection and requirement of norepinephrine to maintain a mean arterial pressure of more than 65 mm Hg despite adequate fluid resuscitation.

2.2. Patient management

The hemodynamic management of patients with septic shock in our ICU follows a standard protocol that includes the optimization of volemia with isotonic saline to achieve central venous pressure of 8 to 12 mm Hg [1], the titration of norepinephrine to maintain a mean arterial pressure more than 65 mm Hg. Norepinephrine therapy was tapered with ongoing hemodynamic stabilization, keeping the mean arterial pressure above 65 mm Hg, until cessation of vasopressor support was possible. If low cardiac output was detected by means of echocardiography or thermodilution monitoring, dobutamine was added. A urinary output higher than 0.5 mL/kg per hour is a goal of hemodynamic resuscitation. Steroids were prescribed according to the decision of the primary physician. Patients treated with steroids received the first dose immediately after corticotropin test. Hydrocortisone was administered intravenously every 6 hours as a 50-mg bolus. One tablet containing 0.05 mg of fludrocortisone was administered daily through a nasogastric tube with 20 ml of water when enteral feeding was possible. Steroid treatment duration was 7 days.

2.3. Adrenal function studies

Blood samples to measure baseline and stimulated cortisol samples at 30 and 60 minutes after injecting 250 μg adrenocorticotropin hormone (ACTH) (Synacthene, Novartis, Switzerland) [7] were obtained in all patients within 72 hours of septic shock onset. Whole blood was collected into crystal tubes without anticoagulant to measure cortisol. Samples were immediately centrifuged and stored at −20°C until measurement. Serum cortisol was measured using an immunochemiluminescent assay—cortisol (Advia, Centaour, Bayer, NY). Reference values for nonstressed individuals in our reference laboratory were 4.3 to 24.4 μg/dL.

2.4. Definitions

Septic shock was diagnosed as in previous studies [8,15,16], including (*a*) a proven or highly suspected infection; (*b*) 3 or more of the following conditions: mechanical ventilation, heart rate higher that 90 beats per minute, temperature of more than 38°C or less than 36°C, white blood cell count higher than 12 000 cells/μL or less than 4000 cells/μL; (*c*) sepsis-induced hypotension, defined as systolic blood pressure less than 90 mm Hg or a reduction higher than 40 mm Hg from baseline in the absence of other causes of hypotension. Shock reversal was considered when norepinephrine was discontinued for at least 24 hours [6,8]. Time to shock reversal was calculated from the initiation of norepinephrine therapy until cessation. Severity of illness was evaluated by the Simplified Acute Physiology Score II (SAPS II) [17] and the maximum Sepsis-Related Organ Failure Assessment (SOFA) scores [18]. Relative adrenal insufficiency (RAI) was defined by a response after corticotropin test of 9 μg/dL or less [7].

2.5. Statistical analysis

For continuous variables, the mean and SD are reported, whereas for categorical variables, the number of patients in

each category and the corresponding percentages are given. Differences were compared between groups using the independent Student t test or Mann-Whitney U test (for continuous variables) or χ^2 or Fisher exact test (for categorical variables) when appropriate.

Because of steroid use was not randomly assigned in this patient population, potential confounding and selection biases were accounted for by developing a propensity score for steroid use [19]. Propensity score was calculated through a logistic regression model created with all independent baseline demographic and clinical characteristics of patients, which reached a predetermined level of statistical significance ($P < .15$), and treatment with steroids, as the dependent variable. Propensity scores ranged from 0.032 to 0.996 and reflected each patient's conditional probability of being treated given baseline characteristics. The area under the receiver operating characteristic curve was 0.81, indicating a good discriminatory power of the final model.

The effect of steroid treatment on time to vasopressor therapy withdrawal was estimated, first, from Kaplan-Meier curves and log-rank test for median time, and second, from adjusted Cox proportional hazards regression models using propensity score and other covariates. Corresponding hazard ratios (HRs) along with their 95% confidence intervals (CIs) were reported. Patients who died before vasopressor therapy could be withdrawn and were treated as censored. The effect of steroid treatment on inhospital mortality probability was estimated from logistic regression analysis including propensity score as continuous variable. Corresponding adjusted odds ratios (ORs) along with their 95% CIs were reported. A P value less than .05 was considered significant. Data were analyzed using SPSS statistical package version 11.0 (SPSS Inc, Chicago, Ill).

Table 1 Clinical characteristics of patients with septic shock treated with hydrocortisone (steroid group) and without hydrocortisone (control group)

	Steroid group (n = 124)	Control group (n = 79)	P
Female sex (no. [%])	37 (29.8)	26 (32.9)	.64
Age (y)	61 ± 15	62 ± 14	.61
Body weight (kg)	76 ± 16	76 ± 20	.42
SAPS II	49 ± 15	44 ± 16	.02
Comorbidities			
Diabetes mellitus	20 (16.1)	18 (22.8)	.24
Chronic pulmonary disease	32 (25.8)	25 (31.6)	.37
Cardiac disease	23 (18.5)	15 (19.0)	.94
Chronic liver disease	18 (14.5)	10 (12.7)	.84
Chronic renal disease	6 (4.8)	9 (11.4)	.08
Malignancy	18 (14.5)	12 (9.7)	.90
Steroids therapy <1 y	16 (12.9)	5 (6.3)	.16
Infection site (no [%])			.24
Respiratory	65 (52.4)	39 (49.4)	
Abdominal	39 (31.4)	23 (29.1)	
Urinary	6 (4.8)	10 (12.7)	
Other	14 (11.3)	7 (8.9)	

Table 2 Basal cortisol and cortisol response to the high-dose corticotropin stimulation test of patients with septic shock treated with hydrocortisone (steroid group) and without hydrocortisone (control group)

	Steroid group (n = 124)	Control group (n = 79)	P
Basal cortisol (μg/dL)	22.1 ± 13.3	20.2 ± 10.5	.33
30-min post-HDCST cortisol (μg/dL)	27.4 ± 13.7	28.1 ± 14.1	.67
60-min post-HDCST cortisol (μg/dL)	29.3 ± 13.9	30.2 ± 14.5	.50
Post-HDCST cortisol Δ ≤9 μg/dL (n [%])	83 (66.9)	45 (57.0)	.15

3. Results

From the 203 patients studied, 124 were treated with steroids (steroid group) and 79 were not (control group). Fifty-two patients of steroid group were also treated with fludrocortisone. Septic shock patients treated with or without steroids showed similar baseline clinical characteristics, except for severity of illness evaluated by SAPS II score that was higher in the steroid group than in the control group (Table 1). The main infection site responsible for septic shock was the respiratory tract (51.2 %) (Table 1). ACTH testing was performed within 24 hours of initiation of norepinephrine (NE) in 74% of patients in the steroid group and 67% in the control group ($P = .34$).

Steroid and control groups presented similar baseline and stimulated cortisol values after HDCST, and the incidence of RAI showed no significant differences (Table 2). Albumin levels at the time of ACTH stimulation were similar between the steroid and control group (20.6 ± 5.4 vs 21.2 ± 5.3 g/dL, $P = .48$). The level of norepinephrine when ACTH testing was performed was higher in steroid group than control group (1.04 ± 0.8 vs 0.75 ± 0.7 μg/kg per minute, $P < .001$), and maximum SOFA was higher in the steroid group than in control group (13.6 ± 3.1 vs 12.3 ± 3.2, $P = .003$). Inadequate empirical antibiotic therapy was detected in 15 patients (12.1%) of the steroid group and 6 patients (7.6%) of the control group ($P = .35$).

Median time to vasopressor therapy withdrawal was 11 days in the steroid group and 7 days in the control group ($P = .16$). Cox regression models showed no differences between steroid and control group in time to shock reversal. The HR of remaining on shock in an unadjusted model was 0.77 for patients treated with steroids, and adjusted for the severity of illness evaluated with maximum SOFA, the HR was near 1, without changes including the propensity score

Table 3 Cox proportional hazards analysis of time to shock among patients using steroids

	HR (95% CI)	*P*
Unadjusted	0.77 (0.54-1.11)	.16
Adjusted for maximum SOFA	0.98 (0.67-1.44)	.93
Adjusted for maximum SOFA and inadequate antibiotic	1.04 (0.71-1.53)	.82
Adjusted for maximum SOFA, inadequate antibiotic and propensity score	1.15 (0.71-1.86)	.56

model (Table 3 and Fig. 1). Other covariates as age, SAPS II, baseline, stimulated and delta cortisol values response, and associated use of fludrocortisone were not correlated with shock reversal.

The mortality during shock was similar in both groups: 45.2% (95% CI, 36.4-53.9) in the steroid group vs 34.2% (95% CI, 23.7-44.6) in the control group. Adjusted by age and maximum SOFA score, the OR for steroids was 1.3 (95% CI, 0.7-2.5).

No differences were found in the inhospital mortality of both groups: 62.1% (77 patients; 95% CI, 53.6-70.6) in steroid group vs 51.9 % (41 patients; 95% CI, 40.9-62.9) in control group ($P = .84$). Logistic regression analysis with propensity score did not show differences between steroid and control group in the inhospital mortality. Predictors of inhospital mortality were age, maximum SOFA score, and inadequate antibiotics (Table 4). Previous steroid treatment on the last year, baseline, stimulated and delta cortisol levels, and use of fludrocortisone were not related with inhospital mortality.

4. Discussion

The main findings of this study were that treatment with LDST did not modify the duration of shock and the mortality of septic shock patients.

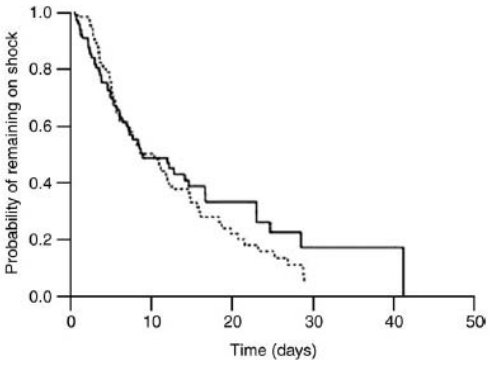

Fig. 1 Survival curves reflecting the probability of remaining on shock. Dashed line represents steroid group; solid line represents control group.

Table 4 Multivariate logistic regression analysis of covariates for mortality adjusted propensity score

	OR (95% CI)	*P*
Age (y)	1.05 (1.02-1.08)	<.001
Maximum SOFA	1.29 (1.15-1.45)	<.001
Inadequate antibiotic	10.8 (2.26-52.0)	.003
Steroid therapy	0.80 (0.37-1.74)	.57
Propensity score	4.33 (0.97-19.3)	.06

Effects of corticosteroids on circulatory response in critically ill patients are known although not fully understood. By elevating cortisol levels, the body attempts to adapt to stress associated with critical illness [15]. Cortisol apparently contributes to maintain cardiac contractility, vascular tone and blood pressure by mediating and enhancing the action of angiotensin II, epinephrine, and norepinephrine [2-6,8,12,20]. The study by Annane et al [7] showed a reduced time to shock reversal and a lower mortality in septic shock patients with relative adrenal insufficiency when they were treated with LDST. However, this study has been criticized; because the biochemical diagnosis of RAI is not clear [3-5,12,14,15], most patients previously received etomidate, a well-known agent which interferes in steroidogenesis [21], and moreover, patients with preserved adrenal response in the study who were treated with LDST showed a trend to an increased mortality and no differences in time to shock reversal [7]. Different trials [6,7,22,23] and meta-analyses [24,25] showed that LDST in septic shock patients was associated to a beneficial effect in shock reversal. The surviving sepsis campaign guidelines [1], following previously cited studies, support LDST use in vasopressor-dependent septic shock patients. However, its widespread use in this setting has been recently criticized [5,12-14].

In our study, patients treated with steroids presented higher vasopressor requirements, and time to shock reversal was longer than in control group. However, when both groups were adjusted by maximum SOFA score, this difference was reduced to 2%. When we adjusted by the propensity score, these results were not significantly modified. In summary, our results showed that time to shock reversal depended on the severity of illness, and this probably constitutes a key factor in our results. The (nonsignificant) higher mortality found in the steroid group (62% vs 52%, $P = .84$) concurs with these findings. In addition, we observed that the variables related to mortality were age, maximum SOFA score, and inadequate empirical antibiotic treatment, which are well-known factors related with outcome in septic shock patients [17,26,27]. Our results are in dissonance with previous studies on LDST use in septic shock patients, as we did not find differences in time to shock reversal when steroids were used or not. A possible explanation of our results is based on the retrospective design of the study and the fact that it was difficult to compare the times patients received LDST or would have received LDST (in the control group). However, a similar percentage of patients in both groups were tested for cortisol response

within 24 hours of treatment with NE. In addition, the patients included in the studies by Briegel et al [6] and Bollaert et al [22] had a lower severity of illness, as reflected by a lower mortality than in our study, and in our population, we found that the severity of illness was strongly correlated with time to achieve shock reversal. In the study by Annane et al [7], time to shock reversal was shorter in patients treated with steroids. These results are influenced by the high incidence of nonresponder patients (76%) found in the study; as in the group of patients with a preserved adrenal response, no differences in time to shock reversal were found. Regarding 28-day, ICU, or inhospital mortality, differences on mortality were found to be statistically significant only when the group of nonresponders to the corticotropin test was considered.

The HDCST has been used in many centres to determine which patients present adrenal impairment. However, this test has been criticized because it represents a supraphysiological stimulation of the adrenal gland [15], its results are poorly reproducible [28], and in addition, a significant variability in the interpretation of the results depending on the immunoassays used has been recently suggested [29]. Because of it, several authors support the use of the low-dose (1 μg) stimulation test [30], which also has been criticized [31]. Baseline cortisol have been also correlated with adrenal status, and minimal values suggested to maintain a "normal" adrenal function in the critically ill patients range from 10 to 34 μg/dL [3,5,10,32]. In our study, baseline, stimulated or delta cortisol values were not correlated with time to shock reversal or inhospital mortality.

We would like to discuss several limitations of our study: the most important is that this is not a randomized controlled trial, which is the optimal design to demonstrate cause and effect. However, epidemiological studies using an adjusted propensity score analysis can provide valuable information [19]. The second limitation is the retrospective nature of the analysis and the number of patients included. Finally, we did not measure corticosteroid-binding globulin, and although the albumin levels were similar in both groups of patients, the free cortisol index was not calculated [33]. However, its use in daily clinical practice remains limited in our environment because it is laborious and expensive [15].

In conclusion, our results raise concerns about the use of LDST in septic shock patients, as the main results were that septic shock patients treated with LDST showed similar time to shock reversal and mortality than patients not treated with steroids. Prospective randomized controlled studies should determine if septic shock patients would benefit from low dose steroid therapy.

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Commentary

Corticosteroids for sepsis: Controversial forever?

Endogenous release of cortisol is a paramount step in host response to infections. Almost a century ago, people recognized necrosis or hemorrhage as being a lethal complication of sepsis [1]. Several decades later, it was demonstrated that an intact adrenal cortex, that is, normal production of cortisol, is essential to survive sepsis [2]. How cortisol modulates inflammation and its effects on the cardiovascular system are now well established. Basically, mechanisms of action of cortisol involve genomic interactions mainly counterbalancing the nuclear factor κB pathway and nongenomic effects. The latter effects are yet not fully understood and likely include overexpression of endothelial nitric oxide synthase and intracellular mobilization of calcium [3]. It is thought that corticosteroid-enhanced endothelial nitric oxide synthesis increases tissue perfusion and limits tissue damage during ischemia [4]. Corticosteroid effects on smooth muscle's intracellular calcium likely affect systemic vascular resistance. Indeed, hypotension and unresponsiveness to α-agonists is the hallmark of Addison crisis, and hypertension is common in Cushing syndrome. In septic animals, endogenous cortisol was shown to account for the cardiovascular tolerance to endotoxin [5]. In endotoxin-challenged healthy volunteers [6] as well as in patients with septic shock [7], a low dose of corticosteroids (50-100 mg of hydrocortisone) was shown to rapidly (within 1 hour) restore vascular responsiveness to norepinephrine, an effect that was not mediated by inducible nitric oxide synthase or cyclooxygenase II activities. Subsequently, 7 randomized controlled trials, accounting for 995 cases of septic shock, demonstrated that 100 to 300 mg of hydrocortisone, IV, hastened shock reversal, and the relative risk (RR) of being weaned from vasopressors at 1 week was 1.40 (95% confidence interval, 1.26-1.56) in favor of corticosteroids [8]. Yet, in this issue of the journal, Raurich and colleagues[9] did not find any benefit of low-dose hydrocortisone in their patients. However, this was a retrospective study, and therefore, it is impossible to determine the reason why corticosteroids failed to improve patients' cardiovascular status. Obviously, this study cannot cast any doubt on the conclusions from both knowledge on the mechanisms of action of corticosteroids and the results of high-quality randomized, double-blind, placebo-controlled trials. It is noteworthy that the efficacy and safety of corticosteroids in sepsis have been investigated in randomized controlled trials for half a century, and still, this treatment remains controversial. When one looks carefully at all randomized controlled trials (accounting for 2700 patients), one can draw the following conclusions: (1) a short course of high-dose corticosteroids has no effect on survival (RR, 0.99; 95% CI, 0.83-1.17); and (2) a long course (5 days or more at full dose) of low daily doses (300 mg or less of hydrocortisone or equivalent) improves survival (RR, 0.87; 95% CI, 0.76-0.99). The results were very consistent across studies of low-dose corticosteroids (test for heterogeneity: $P = .43$ and $I^2 = 0.7\%$). The sickest patients, such as those poorly responsive to fluids and vasopressors, are more likely to benefit from hydrocortisone, and the hemodynamic response in these patients is more likely to influence mortality than it is in patients rapidly stabilized with fluids or vasopressors. It is this author's opinion that all patients with septic shock who failed to improve (ie, could not be weaned from vasopressors) after 6 hours of appropriate hemodynamic resuscitation [10] should be treated with low-dose corticosteroids.

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Respuesta hemodinámica precoz a los corticoides en el shock séptico

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Objetivo. **El tratamiento con corticoides a dosis bajas (LDST) en los pacientes con shock séptico tratados con soporte vasoactivo se ha asociado a una disminución del tiempo de shock. Los pacientes con cortisol basal disminuido o con respuesta anormal a la estimulación suprarrenal deberían tener un mayor beneficio con los LDST, por lo que hemos estudiado la respuesta hemodinámica precoz en pacientes con shock séptico tratados o no con LDST.**

Diseño. **Estudio retrospectivo.**

Ámbito. **Unidad de cuidados intensivos (UCI) en un hospital universitario de tercer nivel.**

Pacientes. **Estudiamos a 96 pacientes ingresados en la UCI, distribuidos en dos grupos de 48 pacientes según hubieran recibido corticoides (grupo A) o no (grupo B), apareados según los valores de cortisol basal y los requerimientos de noradrenalina.**

Intervenciones. **A todos los pacientes, se realizó un test de estimulación suprarrenal con 250 μg de corticotrofina en las primeras 72 h del inicio del shock.**

Variables principales de interés. **Cortisol basal, incremento de cortisol, cortisol máximo, reducción de la dosis de noradrenalina, duración del shock.**

Resultados. **Ambos grupos fueron comparables. Las cifras de cortisol basal antes del test de estimulación suprarrenal y el cortisol máximo fueron similares en ambos grupos. No hubo diferencias significativas entre ambos grupos en la dosis de noradrenalina antes y a las 24 h tras la estimulación suprarrenal. La reducción en la dosis de noradrenalina a las 24 h no se correlacionó con las cifras de cortisol basal ni con la respuesta a la estimulación suprarrenal.**

Conclusiones. **El tratamiento con LDST no se asoció a una mejoría hemodinámica a las 24 h, independientemente de las cifras de cortisol basal y de la respuesta a la estimulación suprarrenal.**

PALABRAS CLAVE: *Cortisol. Shock séptico. Respuesta hemodinámica. Insuficiencia suprarrenal. Corticoides.*

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IMMEDIATE HEMODYNAMIC RESPONSE TO STEROID TREATMENT IN SEPTIC SHOCK

Objective. **Treatment with low dose steroids (LDST) in patients with septic shock treated with vasoactive agents has been related to earlier shock reversal. Patients with low baseline cortisol and a blunted response to the corticotropin test are more likely to benefit from LDST, so we compared the immediate hemodynamic response in patients with septic shock who received LDST with that of those who did not receive LDST.**

Design. **Retrospective study.**

Scope. **Intensive Care Unit (ICU) of a tertiary university hospital.**

Patients. **We studied 96 patients admitted to the ICU. Patients were classified in two groups of 48 patients: group A received LDST and group B did not; patients were matched according to baseline cortisol levels and norepinephrine requirements.**

Interventions. **All patients underwent a short corticotropin test (250 μg ACTH) within 72 h of septic shock onset.**

Main variables of interest. **Baseline cortisol, delta cortisol, peak cortisol, norepinephrine reduction after LDST, and duration of shock.**

Results. **The two groups were comparable: baseline and stimulated cortisol levels before corticotropin test were similar, and there were no differences in the norepinephrine dose before and 24 h after testing adrenal response (p = 0.98 and p = 0.53, respectively). Norepinephrine reduction at 24 h after testing was not correlated with baseline cortisol or with adrenal response to the corticotropin test.**

Conclusions. **LDST was not associated to improved 24-hour hemodynamic response, irrespective of the baseline and stimulated cortisol levels.**

KEY WORDS: *Cortisol. Septic shock. Hemodynamic response. Adrenal insufficiency. Steroids.*

INTRODUCCIÓN

Las guías de la Surviving Sepsis Campaign recomiendan el uso de hidrocortisona a dosis de 200-300 mg/día (*low dose steroid therapy* [LDST]) en los pacientes con shock séptico que necesitan tratamiento con fármacos vasoactivos[1].

Diversos estudios indican que el cortisol, a través de diversos mecanismos, es determinante para mantener la contractilidad cardíaca, el tono vascular y la presión arterial[2-4]. Estudios recientes indican que los enfermos con shock séptico dependientes de soporte vasoactivo deben ser tratados con LDST para conseguir una mejoría hemodinámica y una reducción del tiempo de shock[1,5-8]. Sin embargo, no está bien determinado qué cifras de cortisol deben considerarse óptimas en el shock séptico (se han propuesto valores basales entre 10 y 34 μg/dl) y, además, no se ha precisado con exactitud si el tratamiento con LDST debe realizarse según los valores basales de cortisol o dependiendo del resultado tras una prueba de estimulación dinámica suprarrenal[9-11].

Diversos autores recomiendan iniciar el tratamiento con LDST en los pacientes con inestabilidad hemodinámica, independientemente de las cifras de cortisol[12,13]. Una adecuada respuesta hemodinámica precoz sería el mejor indicador de disfunción suprarrenal[12,13]. Recientemente hemos revisado el impacto de los LDST en los pacientes con shock séptico ingresados en nuestra unidad de cuidados intensivos (UCI) en una muestra de 203 pacientes, y no hemos hallado relación con la mortalidad ni con el tiempo de shock[14]. Por todo ello, consideramos que no se ha establecido con claridad qué grupos de pacientes podrían beneficiarse del tratamiento con LDST.

Los pacientes con cifras bajas de cortisol basal y los que no responden a la estimulación suprarrenal con corticotrofina cuando se los trata con LDST deberían presentar una mejor respuesta hemodinámica que los no tratados con LDST. Por lo tanto, hemos estudiado la respuesta hemodinámica a las 24 h en pacientes con shock séptico, tratados o no con LDST.

PACIENTES Y MÉTODOS

Se seleccionó a 162 pacientes de una base de datos de pacientes con shock séptico recogida de modo retrospectivo. Entre ellos, 103 fueron tratados con LDST y 59 no recibieron corticoides. La decisión de tratar o no con LDST correspondió al médico intensivista responsable de cada paciente. Se excluyó del análisis a los pacientes que previamente habían recibido medicación que pudiera interferir en el metabolismo del cortisol (corticoides previos, etomidato, ketoconazol) y a las pacientes embarazadas. Se apareó a los restantes para que recibieran LDST o no, de acuerdo con intervalos de cortisol basal de 5 μg/dl y a las dosis de noradrenalina (NA) en diferencias inferiores al 20%, con lo que resultó un total de 96 pacientes. De este modo, se analizó retrospectivamente a 96 pacientes con shock séptico ingresados en la UCI de nuestro hospital entre abril de 2003 y noviembre de 2005. El comité de investigación de nuestro centro aprobó el estudio y consideró innecesario obtener el consentimiento informado, al tratarse de un estudio observacional y retrospectivo.

Todos los pacientes recibieron NA para mantenerse estables hemodinámicamente. La función suprarrenal se evaluó utilizando el test de estimulación suprarrenal con 250 μg de corticotrofina. Se trató con LDST (50 mg de hidrocortisona intravenosa cada 6 h y 0,05 mg de fludrocortisona cada 24 h por vía oral cuando la vía digestiva funcionaba correctamente) a 48 pacientes (grupo A), al igual que en el estudio de Annane et al[7]. Como grupo control (grupo B), seleccionamos a 48 pacientes con shock séptico a los que se realizó un test de estimulación suprarrenal pero no recibieron tratamiento con LDST.

El tratamiento hemodinámico de estos pacientes siguió un protocolo preestablecido, previamente detallado[14], que incluye la optimización de la volemia, el empleo de NA para conseguir una presión arterial media (PAM) > 65 mmHg y soporte inotrópico con dobutamina si se detectaba disfunción cardíaca asociada. Uno de los objetivos era conseguir una diuresis > 0,5 ml/kg/h.

Se documentó la dosis de NA necesaria antes y a las 24 h de la realización del test de estimulación suprarrenal, así como el tiempo total de tratamiento con NA. La gravedad de los pacientes se evaluó con los siguientes índices de gravedad: Simplified Acute Physiology Score II (SAPS-II)[15], Acute Physiology and Chronic Health Evaluation II (APACHE II)[16] y el Sepsis-related Organ Failure Assesment (SOFA)[17] a las 24 h de ingreso y el valor máximo durante la primera semana del shock séptico. También se recogieron datos respecto al número de pacientes tratados con ventilación mecánica, terapias de reemplazo renal y empleo de drotrecogina alfa. Además, se documentó el número de pacientes que recibieron tratamiento antibiótico inadecuado y el balance hídrico de

las primeras 24 h, sin contabilizar las pérdidas insensibles.

De todos los pacientes se obtuvieron muestras de sangre periférica a través de un catéter arterial para determinar el cortisol basal y a los 30 y los 60 min tras la estimulación de la glándula suprarrenal con 250 µg de corticotrofina (Synacthen) durante las primeras 72 h de la instauración del shock séptico.

Las muestras se recogieron en tubos sin anticoagulante para determinar cortisol, se centrifugaron inmediatamente y se almacenaron a –20 °C hasta su análisis. El cortisol sérico se analizó mediante un análisis de inmunoquimioluminiscencia directa en analizador Advia, Centaour (Siemens, M.S. Diagnostics). Los valores de referencia en sujetos sanos en nuestro laboratorio son 4,3-24,4 µg/dl. El límite de detección es de 0,2 µg/dl, la recuperación a distintos niveles se sitúa entre el 86,2 y el 114%, con una media del 101%. La imprecisión intraanalítica oscila entre el 2,89 y el 3,62%, y entre análisis, entre el 1,86 y el 5,45% en relación con el nivel analizado.

Se diagnosticó shock séptico de acuerdo con los criterios de la International Consensus Conference Definition[18]. La insuficiencia suprarrenal relativa (ISR) se diagnosticó en los pacientes con un incremento < 9 µg/dl de sus concentraciones de cortisol respecto a las basales tras la estimulación con corticotrofina[7]. Se consideró cese del shock cuando se suspendieron los fármacos vasoactivos[5,6]. La respuesta hemodinámica precoz se evaluó a las 24 h de la estimulación glandular suprarrenal.

El desenlace principal del estudio es la variación en la dosis de noradrenalina a las 24 h de iniciarse o no el tratamiento con corticoides. Como variables secundarias, se evaluó la mortalidad hospitalaria y el tiempo de shock.

Análisis estadístico

Los datos se presentan como media y desviación estandar. Las diferencias entre los grupos se analizaron utilizando la prueba de la χ^2 o la exacta de Fisher para las variables categóricas y la de la t de Student o la U de Mann-Whitney para las variables continuas. Evaluamos la duración del shock séptico utilizando el método de Kaplan-Meier y comparamos los grupos con el *log-rank test*. Un valor de $p < 0,05$ fue indicativo de significación estadística. Los datos se analizaron utilizando SPSS statistical package version 13.0 (SPSS Inc., Chicago).

RESULTADOS

Los pacientes de ambos grupos presentaban en el momento de ser incluidos iguales características clínicas y demográficas, gravedad del shock séptico, comorbilidades, incidencia de pacientes posquirúrgicos y foco infeccioso (tabla 1).

El tiempo transcurrido entre el diagnóstico de shock séptico y la realización del test de estimulación suprarrenal fue de 1,5 ± 2,6 días en el grupo tratado con LDST y 1,3 ± 2,1 días en el grupo control (p = 0,61). Ambos grupos presentaron similares valores de cortisol basal, valor máximo de cortisol tras administrar 250 µg de corticotrofina e incidencia de ISR (tabla 2). Las cifras de albúmina sérica el día en que se realizó la estimulación suprarrenal fueron similares en ambos grupos (grupo A, 20,9 ± 4,7 g/dl; grupo B, 21,5 ± 5,2 g/dl; p = 0,52).

Las dosis de NA antes y a las 24 h de la estimulación suprarrenal fueron similares en ambos grupos, así como la diferencia de NA (tabla 3). La reducción de la dosis de NA a las 24 h no guardó relación con las cifras de cortisol basales (fig. 1) ni con la respuesta suprarrenal tras la estimulación con corticotrofina (tabla 4). Las curvas de Kaplan-Meier no demostraron diferencias entre ambos grupos en el tiempo de tratamiento con NA (mediana en el grupo A, 7 días; grupo B, 8 días; p = 0,99).

No hubo diferencias entre ambos grupos en la incidencia de pacientes tratados con ventilación mecá-

TABLA 1. Características de los pacientes con shock séptico incluidos en el estudio

	Grupo A (n = 48)	Grupo B (n = 48)	p
Varones/mujeres	33/15	30/18	0,52
Edad (años)	62 ± 15	61 ± 14	0,66
Peso (kg)	75 ± 15	76 ± 19	0,72
SAPS II	46 ± 13	43 ± 15	0,24
APACHE II	21 ± 5	20 ± 8	0,76
SOFA (primeras 24 h)	11,1 ± 2,6	10,7 ± 3,3	0,52
Comorbilidad			
Diabetes mellitus	7 (14,6)	11 (22,9)	0,3
EPOC	12 (25)	10 (20,8)	0,63
Afección cardíaca	10 (20,8)	8 (16,7)	0,6
Hepatopatía crónica	4 (8,3)	6 (12,5)	0,5
Insuficiencia renal crónica	3 (6,2)	4 (8,3)	1
Neoplasias	8 (16,7)	6 (12,5)	0,56
Uso de corticoides < 1 año	6 (12,5)	5 (10,4)	0,75
Foco infeccioso			0,41
Respiratorio	27 (56,2)	25 (52,1)	
Abdominal	15 (31,2)	14 (29,2)	
Urinario	2 (4,2)	6 (12,5)	
Otro	4 (8,3)	3 (6,2)	
Quirúrgicos	15 (31,3)	12 (25)	0,5

APACHE: Acute Physiology and Chronic Health Evaluation; EPOC: enfermedad pulmonar obstructiva crónica; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment.
Grupo A: pacientes tratados con corticoides; grupo B: grupo control.
Los resultados expresan media ± desviación estándar o n (%)

TABLA 2. Cortisol basal y tras estimulación glandular con 250 mg de corticotrofina en ambos grupos

	Grupo A (n = 48)	Grupo B (n = 48)	p
Cortisol basal (µg/dl)	22 ± 12,3	21,7 ± 12	0,92
Cortisol (µg/dl) a los 30 min de HDCST	28,2 ± 13,6	28,9 ± 12,1	0,79
Cortisol (µg/dl) a los 60 min de HDCST	29,7 ± 13,7	30,6 ± 12,3	0,74
Diferencia de cortisol ≤ 9 µg/dl tras HDCST	31 (64,6)	24 (50)	0,18

HDCST: prueba de estimulación con altas dosis de corticotrofina.
Grupo A: pacientes tratados con corticoides; grupo B: grupo control.
Los datos expresan media ± desviación estándar o n (%).

TABLA 3. Dosis de noradrenalina antes y a las 24 h de la estimulación suprarrenal

	Grupo A (n = 48)	Grupo B (n = 48)	p
Noradrenalina basal (μg/kg/min)	0,60 ± 0,37	0,59 ± 0,35	0,88
Noradrenalina a las 24 h (μg/kg/min)	0,41 ± 0,38	0,39 ± 0,42	0,53
Noradrenalina diferencia (μg/kg/min)	0,19 ± 0,36	0,20 ± 0,36	0,96

HDCST: prueba de estimulación con altas dosis de corticotrofina.
Grupo A: pacientes tratados con corticoides; grupo B: grupo control.
Los datos expresan media ± desviación estándar salvo que se indique otra cosa.

nica, terapias de reemplazo renal y drotrecogina alfa (tabla 5). Tampoco hallamos diferencias en el número de pacientes que recibieron tratamiento antibiótico inadecuado ni en el balance hídrico a las 24 h (tabla 5).

El SOFA máximo fue más elevado en el grupo A que en el grupo B (13,4 ± 3,2 y 12,0 ± 3,5 respectivamente; p = 0,054). No hallamos diferencias significativas en la mortalidad hospitalaria entre ambos grupos (el 54% en el grupo A y el 52% en el grupo B; p = 0,84).

DISCUSIÓN

Los resultados de nuestro estudio indican que los pacientes con shock séptico tratados con hidrocortisona, independientemente de las cifras basales de cortisol y la respuesta suprarrenal, no presentan una mejor respuesta hemodinámica a las 24 h que los que no reciben dicho tratamiento.

Los efectos de los corticoides en la respuesta cardiovascular, aunque conocidos, no están plenamente comprendidos[19]. El cortisol contribuye a mantener la contractilidad cardíaca, el tono vascular y la presión

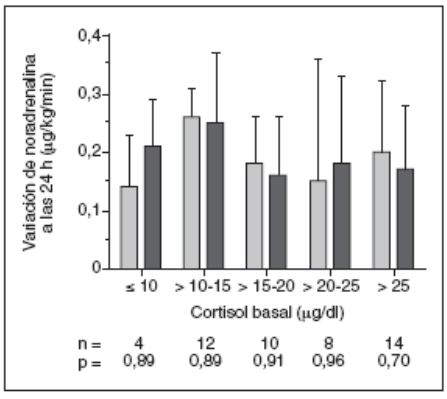

Figura 1. Variación en la dosis de noradrenalina las primeras 24 h en los pacientes tratados con bajas dosis de corticoides (barras grises) y grupo control (barras negras), según las cifras basales de cortisol.

TABLA 4. Diferencias en la respuesta hemodinámica en los pacientes con y sin ISR, según recibieran o no tratamiento con corticoides

	Grupo A (n = 48)	Grupo B (n = 48)	p
Diferencia de cortisol ≤ 9 μg/dl tras HDCST, n	31	25	
NA basal (μg/kg/min)	0,54 ± 0,29	0,56 ± 0,39	0,8
NA a las 24 h (μg/kg/min)	0,38 ± 0,36	0,35 ± 0,44	0,28
NA diferencia (μg/kg/min)	0,16 ± 0,32	0,21 ± 0,41	0,44
Diferencia de cortisol > 9 μg/dl tras HDCST, n	17	23	
NA basal (μg/kg/min)	0,70 ± 0,46	0,62 ± 0,31	0,85
NA a las 24 h (μg/kg/min)	0,45 ± 0,43	0,43 ± 0,40	0,96
NA diferencia (μg/kg/min)	0,25 ± 0,43	0,18 ± 0,31	0,45

Grupo A: pacientes tratados con corticoides; grupo B: grupo control.

arterial aumentando la respuesta a la angiotensina II, la adrenalina y la noradrenalina[2-6,12,20]. Las guías de la Surviving Sepsis Campaign apoyan el uso de la LDST en el shock séptico dependiente de fármacos vasoactivos[1], independientemente del diagnóstico bioquímico[21], basándose en estudios aleatorizados donde el uso de hidrocortisona se ha asociado con menos tiempo de shock[5-8,22] y disminución de la mortalidad[7]. Sin embargo, su uso indiscriminado ha sido criticado[4,10,12], y en nuestra experiencia no se ha relacionado con una disminución del tiempo de shock –que sí se relacionó con la gravedad del cuadro– ni con una disminución de la mortalidad[14]. Por ello, determinar qué grupo de pacientes con shock séptico podrían beneficiarse del tratamiento con LDST es fundamental y sigue sin ser dilucidado[10]. No se debe olvidar tampoco los potenciales efectos adversos asociados al uso de corticoides en los pacientes en la UCI[23].

Teóricamente, los pacientes con shock séptico que presentaran bajas cifras basales de cortisol o no respondieran a la estimulación suprarrenal deberían presentar una mejor respuesta a la LDST. Sin embargo, en nuestro estudio no hemos evidenciado un beneficio inmediato en la evolución hemodinámica (disminución de las dosis de NA a las 24 h) ni en la mortalidad; al igual que Rady et al[24], Keh et al[6] tampoco hallaron diferencias tras 24 h en la dosis de fár-

TABLA 5. Tratamientos aplicados a los pacientes en shock séptico

	Grupo A (n = 48)	Grupo B (n = 48)	p
Ventilación mecánica, n (%)	44 (91,7)	43 (89,6)	1
Hemodiafiltración continua, n (%)	15 (31,3)	18 (37,5)	0,52
Drotrecogina alfa, n (%)	2 (4,2)	5 (10,4)	0,21
Antibiótico inapropiado, n (%)	5 (10,4)	5 (10,4)	1
Balance hídrico a las 24 h (l), media ± DE	2,7 ± 2,3	2,9 ± 2,6	0,59

Grupo A: pacientes tratados con corticoides; grupo B: grupo control.

macos vasoactivos en los pacientes con shock séptico tratados o no con corticoides. Los hallazgos de nuestro estudio no respaldan lo propugnado por algunos autores que indican que una respuesta hemodinámica precoz tras 1-2 días de tratamiento con LDST sería el punto crucial para continuar con dicho tratamiento[10,12,13].

Respecto a los parámetros bioquímicos que se asociarían teóricamente a una mejor respuesta hemodinámica al tratamiento, la controversia es aún mayor[10,12,21], dado que son bien conocidas las limitaciones de las pruebas diagnósticas en los enfermos críticos[25]. Las cifras basales de cortisol consideradas «óptimas» en los pacientes críticos oscilan entre 10 y 34 μg/dl[3,4,8,9,21]. Ante la variabilidad de estas cifras, Marik et al[26], en un estudio que incluyó a 59 pacientes con shock séptico, mostraron que cifras basales de cortisol de 23,7 μg/dl serían el parámetro analítico más preciso para predecir la respuesta hemodinámica a la LDST. En nuestro estudio no hallamos diferencias en la respuesta hemodinámica de acuerdo con diferentes intervalos de cortisol basal. Sin embargo, debe reseñarse que el grupo de cortisol basal < 10 μg/dl sólo incluyó a 8 pacientes. Otros estudios recientes tampoco hallaron relación entre las cifras basales de cortisol, la respuesta hemodinámica y el pronóstico[24,27].

En cuanto a la valoración de la reserva de la glándula suprarrenal, desde el estudio de Annane et al[7], el test de estimulación suprarrenal con 250 μg de corticotrofina se ha utilizado de modo generalizado. Sin embargo, esta prueba ha sido criticada, ya que supone un estímulo suprafisiológico de la glándula suprarrenal[19]. Por ello, algunos autores respaldan la práctica de estimulación suprarrenal con dosis bajas de corticotrofina[28], que presenta una mayor sensibilidad diagnóstica, aunque no haya consenso respecto a su empleo en los pacientes críticos[29]. El estudio de Annane et al[7] mostró una reducción de la mortalidad y el tiempo de shock sólo en los pacientes con ISR. Igualmente, Oppert et al[8] mostraron que los pacientes con una inadecuada reserva suprarrenal presentaban una mejor respuesta hemodinámica cuando se los trataba con hidrocortisona, a diferencia del estudio de Bollaert et al[22], que hallaron un beneficio hemodinámico en los pacientes sépticos con y sin ISR. Otros autores han señalado que la estimulación glandular no predice la respuesta hemodinámica y recomiendan el uso generalizado de corticoides[30].

Nuestro estudio presenta varias limitaciones. La más importante es que se trata de un estudio retrospectivo con un número de pacientes pequeño. Sin embargo, los pacientes estaban bien apareados por diferentes cifras basales de cortisol y requerimientos de fármacos vasoactivos, y ambos grupos presentaban iguales características clínico-demográficas. Otra limitación es que no determinamos las cifras de globulina transportadora de esteroides. Aunque la concentración sérica de albúmina era similar en ambos grupos, no se pudo calcular el índice de cortisol libre, que constituye la porción biológicamente activa[2,25]. Sin embargo, su uso en la clínica práctica actualmente es muy escaso[19].

Concluimos que los pacientes con shock séptico tratados con LDST presentan a las 24 h una respuesta hemodinámica idéntica a la de quienes no reciben dicho tratamiento, independientemente de las cifras basales de cortisol y la respuesta a la estimulación suprarrenal.

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Relationship between plasma adrenocorticotropin hormone and intensive care unit survival in early traumatic brain injury. Llompart-Pou JA, Raurich JM, Ibáñez J, Burguera B, Ayestarán JI, Pérez-Bárcena J. ***J Trauma 2007; 62:1457-61***.

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Relationship Between Plasma Adrenocorticotropin Hormone and Intensive Care Unit Survival in Early Traumatic Brain Injury

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Background: **Hypothalamic pituitary adrenal response has been recently evaluated in patients with traumatic brain injury (TBI) with different results. Our objective was to study this response and its relationship with outcome in the early stage after TBI.**

Methods: **We conducted a prospective observational clinical study in the intensive care unit of a tertiary level university hospital. The study included 50 consecutive patients who suffered isolated TBI. Intracranial pressure (ICP) was measured by an intraparenchymal probe. All patients were sedated and mechanically ventilated. Second-level measures were provided as per protocol, when needed. We measured plasma adrenocorticotropin hormone (ACTH) levels, as well as baseline and stimulated serum cortisol after a high-dose corticotrophin stimulation test, within 2 days after TBI for all patients.**

Results: **Mean age was 36 ± 18 (range 16–77) years. Forty-four (88%) were male. Median Glasgow Coma Scale score was 7. Mean ACTH was 15.4 ± 19.8 pg/mL. Mean baseline cortisol was 14.8 ± 9.0 μg/dL and mean stimulated cortisol was 27.1 ± 7.3 μg/dL and 30.5 ± 7.2 μg/dL at 30 and 60 minutes, respectively. Baseline and stimulated cortisol were not correlated with mortality. Logistic regression analysis revealed that, either plasma ACTH levels <9 pg/mL or lack of indication to provide second-level measures to control ICP were significant independent predictors of survival.**

Conclusions: **The presence of a low plasma ACTH concentration at an early stage of TBI and lack of indication to provide second-level measures to control ICP were associated with a higher intensive care unit survival.**

Key Words: **Traumatic brain injury, Plasma adrenocorticotropin, Cortisol, Outcome.**

J Trauma. 2007;62:1457–1461.

Traumatic brain injury (TBI) constitutes an important cause of death in young adults.[1] Prognosis in patients who suffer a TBI has been mainly related to clinical signs, such as Glasgow Coma Scale (GCS) score[2] and pupil reactivity,[3] and to cranial computed tomography scan features at admission.[4]

The existence of neuroendocrine dysfunction in TBI patients has long been recognized and an increased attention in the hypothalamic-pituitary-adrenal (HPA) axis has been documented.[5–7] However, although current understanding suggests that after trauma there is an increase in total serum cortisol, plasma adrenocorticotropin hormone (ACTH) and catecholamines,[6,8] there remains considerable controversy concerning plasma cortisol and cortisol dynamics in the acute and intermediate phases after brain injury.[9] These differences come from different causes of brain injury,[7] severity of injury,[10,11] and time of study after injury.[11–13]

The relationship between plasma ACTH and cortisol levels and patient outcome in TBI patients is not well known. Woolf et al.[14] reported that admission cortisol levels in TBI patients were elevated in all patients, irrespective of the severity of the brain injury. Those patients with serum cortisol values <20 μg/dL 1 day after injury, had better neurologic outcomes than did those who had higher cortisol values. Koiv et al.[15] reported that plasma ACTH levels were relatively low in patients with severe TBI, in disagreement with the high serum cortisol concentration in these patients.

The aim of our study was to determine plasma ACTH levels and the adrenal reserve in the early phase of TBI and its relationship to clinical outcome.

MATERIALS AND METHODS

Patients and Management

Fifty consecutive patients with isolated TBI admitted to our intensive care unit (ICU) between July 2003 and May 2005 were prospectively enrolled in this study. We obtained the hospital research ethics committee's approval and the relatives' informed consent. All patients included in the study were intubated, mechanically ventilated, and had intracranial pressure (ICP) monitoring. The exclusion criteria were age

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An abstract containing part of these data has been presented in the 18th ESICM congress in Amsterdam, September 2005.
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<16 years, lack of indication to measure ICP, traumatic injury of other organs, probability of survival <48 hours, previous use of drugs known to affect cortisol secretion (corticosteroids, etomidate), and patients who had developed septic shock.

Immediate removal of intracranial masses was performed when the attending neurosurgeon considered indicated before ICU admission. Management of the patients was done according to a standard TBI protocol used in our ICU. All patients were sedated with midazolam, propofol, or both by continuous intravenous infusion and analgesia was accomplished with morphine. To achieve better ventilation or to improve control of high ICP, muscle paralysis with cisatracurium was induced as required. Norepinephrine (NE) was administered to maintain cerebral pressure perfusion (CPP) above 60 mm Hg when necessary. Treatment of ICP included control of general measures, mannitol, hypertonic saline, and moderate hyperventilation according to jugular bulb oxygen saturation values. Cerebral hemodynamics were evaluated by transcranial color-coded sonography. If second-level measures were required to control high ICP, barbiturate coma or moderate hypothermia was used according to the criteria of the ICU attending physician. When ICP became refractory to second-level measures, we placed an external lumbar drainage if the radiologic conditions detailed in a recent report were present.[16] With this homogeneous management of the patients, we minimized the potential influence of sedation and therapeutic procedures in all patients.

ICP was measured by an intraparenchymal probe (Camino, Integra NeuroSciences, Plainsboro, NJ). Severity of injury at admission was evaluated according to the GCS score after resuscitation,[17] the Injury Severity Score (ISS),[18] and the score of the Acute Physiology and Chronic Health Evaluation II (APACHE II) 24 hours after admission.[19] The degree of head injury was graded radiologically at ICU admission according to cranial computed tomography scan features from a radiologist's point of view, according to Marshall's classification.[20]

Samples

Blood samples for ACTH and cortisol analysis were collected within 2 days of injury onset at different times of the day. Blood samples were obtained through an arterial line. After baseline samples were drawn, a high-dose corticotrophin stimulation test was performed by injecting 250 μg corticotrophin (Synacthene, Novartis, Switzerland). Blood samples were collected 30 and 60 minutes afterward.

The diagnosis of impaired adrenal function reserve was established on the basis of a cortisol response of <9 μg/dL.[21]

Analysis

Whole blood was collected into EDTA crystal tubes with aprotinin to measure ACTH and into crystal tubes without anticoagulant to measure cortisol. Samples were immediately centrifuged and kept cool until measurement. When ACTH analysis was not performed the same day, plasma samples were stored at −70°C.

Plasma ACTH was measured using an immunochemiluminescent assay, ACTH (Immulite 2000, DPC, Los Angeles, CA). Normal values were 9 to 52 pg/mL. The detection limit of the assay was 5 pg/mL. Serum cortisol was measured using an immunochemiluminescent assay, Cortisol (Advia, Centaur, Bayer, NY). Normal values for nonstressed individuals were 4.30 to 24.40 μg/dL.

Statistical Analysis

The values are presented as mean and standard deviation as appropriate. The continuous variables were dichotomized using cut off points that were clinically relevant with previously published threshold values. For the univariate analysis, proportions were compared by the χ^2 test and adjusted odds ratios, and 95% confidence intervals were calculated. To examine the simultaneous effects of multiple variables on ICU survival, a multivariate analysis was performed using a conditional logistic regression model and a forward stepwise selection method to correct for colinearity. Variables were selected for the model if $p < 0.05$. Comparison between groups according to ACTH levels were made using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. A two-tailed p value <0.05 was considered the minimum level of statistical significance. Data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL).

RESULTS

The mean age of the 50 patients studied was 36 ± 18 (range 16–77) years. Forty-four (88%) were male. Median GCS score was 7 (range 3–15). Three patients had an initial GCS score of 14 to 15 but suffered an early and severe deterioration of level of consciousness. All patients had cranial computed tomography (CT) scan abnormalities (Table 1). Mean APACHE II score was 18 ± 6 (range 8–35) and mean ISS was 25 ± 9 (range 11–41). Plasma albumin on the day of the corticotrophin stimulation test was 3.0 ± 0.4 g/dL. Mean time from ICU admission to the corticotrophin test was 29 ± 8 hours. Thirty patients (60%) received NE during the study to maintain CPP above 60 mm Hg. Overall mortality was 26% (13 patients).

Table 1 Distribution of the Patients According to Marshall's Classification and CT Scan at ICU Admission

	Number (%) of Patients
Diffuse lesion type I	0 (0)
Diffuse lesion type II	22 (44)
Diffuse lesion type III	8 (16)
Diffuse lesion type IV	2 (4)
Evacuated mass	13 (26)
Nonevacuated mass	5 (10)

Table 2 Univariate Analysis for Survival

	Odds Ratio	CI 95%	*p*
Age ≤40 yr	2.4	0.67–8.82	0.17
GCS >8 points	2.8	0.67–12.00	0.15
APACHE II ≤15 points	10.2	1.20–86.70	**0.01**
No need of NE	2.8	0.67–11.99	0.15
ACTH ≤9 pg/mL	17.1	3.18–92.12	**<0.0001**
Baseline cortisol ≤20 μg/dL	3.7	0.94–14.40	0.054
Cortisol response >9 μg/dL	1.9	0.39–9.49	0.41
No need second level measures	8.07	1.56–41.72	**0.006**

GCS, Glasgow coma scale; APACHE, acute physiology and chronic health evaluation; NE, norepinephrine; ACTH, adrenocorticotropin hormone.

Bold *p* values indicate statistical significance.

Table 3 The Variables Independently Related to Survival by Multiple Logistic Regression Model

	Odds Ratio	CI 95%	*p*
No need of second-level measures	11.38	1.6–79.0	**0.01**
ACTH ≤9 pg/mL	22.37	3.4–147.4	**0.001**

ACTH, adrenocorticotropin hormone.

Mean plasma ACTH concentration was 15.4 ± 19.8 pg/mL. Thirty patients (60%) had plasma ACTH values lower than 9 pg/mL. Two patients had plasma ACTH concentrations higher than 52 pg/mL. Mean baseline cortisol was 14.8 ± 9.0 μg/dL and stimulated cortisol levels were 27.1 ± 7.3 μg/dL and 30.5 ± 7.2 μg/dL at 30 and 60 minutes, respectively. Eight patients (16%) were nonresponders to the corticotrophin stimulation test, but all of them showed stimulated cortisol at 30 or 60 minutes of >20 μg/dL. ACTH and baseline cortisol were poorly correlated ($r^2 = 0.32$, $p < 0.0001$). Baseline cortisol and maximum stimulated cortisol level showed a better correlation ($r^2 = 0.50$, $p < 0.0001$).

Univariate analysis showed that APACHE II ≤15, no need of second-level measures to control ICP, and plasma ACTH ≤9 pg/mL were correlated with good outcome, whereas GCS score >8, age <40 years, no need of NE to maintain CPP, baseline cortisol <20 μg/dL and cortisol response ≥9 μg/dL were not (Table 2).

Logistic regression analysis showed that no need of second-level measures to control ICP and presence of low plasma ACTH values (<9 pg/mL) at 24 to 48 hours after ICU admission were significant independent predictors of ICU survival (Table 3).

Patients with low ACTH values (<9 pg/mL) had a lower statistically significant mortality than did patients with ACTH values >9 pg/mL (7% vs. 55%, $p < 0.0001$) and a lower baseline cortisol. Consequently, patients with low plasma ACTH and higher survival had an increased ICU length of stay ($p = 0.03$). No significant differences were found with other related variables (Table 4).

DISCUSSION

In this study, we indicate that patients with low plasma ACTH levels at an early stage after TBI had higher ICU survival rates.

The association between cortisol, pituitary hormones deficiencies, severity of TBI, and outcome prediction has been studied with contradictory findings.[6,7,11,22] A good understanding of the HPA axis status in TBI patients is challenging because of the complexity of its different components and its modulation by different hormones and cytokines.[6,23] In addition, both low- and high-dose corticotrophin stimulation tests have been used for ICU patients with brain injury to evaluate adrenocortical function and these tests have been performed at different times after brain injury and under different conditions (sedation, mechanical ventilation).[9,11–13,24,25]

It is commonly accepted that the HPA axis undergoes a biphasic course during severe trauma: a first phase (within 6 days of injury) is characterized by both high ACTH and cortisol levels; the second phase is characterized by a dissociated low plasma ACTH level with a high level of cortisol.[6,8,15,22,26,27] Barton et al.[10] described that a great variability in ACTH concentration exists at initial phases

Table 4 Characteristics of Groups Distributed by ACTH Level

	ACTH ≤9 pg/mL (n = 30)	ACTH >9 pg/mL (n = 20)	*p*
Age, yr*	28 (20–48)	33 (19–52)	0.74
GCS*	7 (5–9)	7 (4–9)	0.54
APACHE II*	16 (13–20)	19 (14–23)	0.18
ISS*	25 (18.25–32.75)	22 (17–36)	0.88
Baseline cortisol (μg/dL)	10.4 ± 5.9	21.4 ± 8.8	**<0.0001**
Cortisol 30′ (μg/dL)	25.6 ± 4.9	29.4 ± 9.7	0.12
Cortisol 60′ (μg/dL)	28.9 ± 5.6	32.8 ± 8.7	0.06
Second level measures, n (%)	14 (47)	12 (60)	0.35
External lumbar drainage, n (%)	3 (10)	3 (16)	0.59
ICU length of stay (days)	20.6 ± 11.0	16.2 ± 15.4	**0.03**
Mortality, n (%)	2 (7)	11 (55)	**<0.0001**

Data expressed as mean ± SD.

* Data expressed as median and interquartile range (25th–75th).

GCS, Glasgow coma score; APACHE, acute physiology and chronic health; ISS, injury severity score.

after TBI, and that its values tended to increase with the severity of injury up to ISS 13 to 24 in the first 2 hours after TBI. This concurs with the results of Penteleny et al.[28] who found that, in patients with head injuries, a fatal outcome could be predicted within the first days if an over-activation of the pituitary-adrenal axis was present. In agreement with these reports, our study reveals low plasma ACTH levels 2 days after TBI in 60% of the patients. This finding was associated with a good outcome prediction. In addition, this subset of patients with low plasma ACTH had a mean baseline cortisol lower than that of the patients with normal or high plasma ACTH (Table 4). It is important to underline that all these patients with low ACTH had a normal adrenal reserve, as evidenced by their optimal response (>20 μg/dL) to the high-dose corticotrophin test.

Our results showed that in the group of patients with low ACTH levels only 2 individuals died; the first one was a 70-year-old man with a nonevacuated mass who presented with cardiac arrest and unexpected hyperkaliemia. He had developed refractory intracranial hypertension and was treated with barbiturate coma when he entered in cardiac arrest. An earlier study described unexpected electrolytes disturbances in patients after therapeutic barbiturate coma.[29] The second patient was a 16-year-old boy who was operated on as a result of a subdural hematoma, and who developed refractory intracranial hypertension. He was treated with moderate intravascular hypothermia and his ICP was controlled. At the rewarming stage, he entered in cardiac arrest and died. Electrolytes disturbances are a well-known side effect after hypothermia therapy.[30] In the group of patients with normal ACTH levels, 11 (55%) died. Among them, nine developed refractory intracranial hypertension as a result of second-level measures failure and subsequently became brain dead. The cause of death in the last two patients was a septic shock.

We understand that our study has several limitations. First, we did not collect blood samples at the same time of the day for all patients and we did a single determination. However, the adrenal circadian rhythm has been suggested to be abolished in patients with brain injuries. In a recent study, Cohan et al.[25] did not find differences between morning and evening cortisol levels. Schwarz et al.,[27] in a small subset of patients suffering from acute space occupying ischemic stroke, also found similar levels of cortisol and plasma ACTH in daily repeated determinations. In addition, recent evidence has shown that random cortisol measurements reflect the 24-hour adrenal secretory profile in patients with sepsis.[31]

Second, some authors think that a low-dose corticotrophin stimulation test is the best method to study adrenal gland function.[11] Incomplete adrenal atrophy in patients with corticotrophin deficiency may be masked by the supraphysiologic dose yielding a misleading normal cortisol response.[32] At the same time, it has been reported that this test is less specific compared with high-dose corticotrophin test.[33] Two previous studies did not find a good correlation between ACTH plasma levels determined during the first days after TBI and outcome.[15,34] However, one of these reports[15] described that patients with severe head injury, and less chance to survive, had very high plasma cortisol levels. Elevated cortisol secretion appears to be more indicative of the severity of trauma and a less favorable clinical outcome.[35]

Another limitation of our study is that we measured total serum cortisol. Corticosteroid binding globulin levels decrease during the acute phase of brain injury,[9] and the calculated free cortisol index could not be correlated with total serum cortisol. However, the use of calculated free cortisol is currently limited in daily clinical practice[25] because measurement of corticosteroid binding globulin is not available in many laboratories, including in ours.

Our data shows that the presence of low plasma ACTH concentrations at an early stage of TBI is associated with a chance of ICU survival. Contrary to what is expected,[36] age was not found to be an independent predictor of outcome in our patients. This fact probably is related to the groups chosen for the analysis (≤40 years) and the small size of the sample. Patients aged >60 years are more likely to have a worse outcome.[36] However, the parameters indicating severity of injury (APACHE II, ISS, GCS, refractory ICP, and need of second-level measures) were equal between both the group with ACTH higher than pg/mL and the group with ACTH lower than 9 pg/mL (Table 4). We could speculate that the hypothalamic pituitary area (where corticotrophin releasing factor is produced), which is the major hormonal coordination center, does a better job integrating afferent signals and predicting the degree of TBI than do traditional markers of prognosis of ICU patients with traumatic brain injuries.

Our findings support the role of plasma ACTH as a prognostic tool for survival in TBI patients. A prospective study evaluating the hypothalamus-pituitary-adrenal axis at different stages after TBI is required.

In summary, in the early stage of isolated and moderate to severe TBI, the presence of low plasma levels of ACTH were associated with significantly increased ICU survival. We think that this data might be considered as a predictor of mortality for TBI patients. At this stage of TBI, in most patients, adrenal gland function, assessed by the high-dose corticotrophin stimulation test, is not impaired.

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ORIGINAL ARTICLE

Acute Hypothalamic–pituitary–adrenal Response in Traumatic Brain Injury with and Without Extracerebral Trauma

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Abstract

Objective Endocrine disturbances are common after traumatic brain injury (TBI). Hypothalamic–pituitary–adrenal (HPA) axis response in TBI patients may be related with hemodynamic status. However, its relationship with outcome is unclear. Our objective was to evaluate HPA axis response in the acute phase after TBI in patients with or without extracerebral trauma (ECT), and to investigate the impact of systemic injury and the mechanisms underlying HPA response.

Methods We prospectively studied 165 patients with moderate to severe TBI. Between 24 and 48 h after TBI, blood samples were taken for plasma adrenocorticotrophin hormone (ACTH) and baseline cortisol measurements. Afterwards, a short corticotrophin hormone test (250 μg Synacthen) was performed and samples were obtained at 30 and 60 min. We compared HPA response in TBI patients presenting with and without ECT and investigate potential mechanisms underlying this response.

Results One hundred and eight patients presented with isolated TBI, whereas 57 patients presented associated ECT. Both groups were comparable. Overall, 23.6% of patients fulfilled adrenal insufficiency (AI) criteria. Patients with plasma ACTH <9 pg/ml and patients presenting with hemorrhagic shock were more likely to present adrenal impairment. Variables associated with mortality were Injury Severity Score, Glasgow Coma Scale, Traumatic Coma Data Bank classification different than type II, need of second level measures to control intracranial pressure and plasma ACTH >9 pg/ml.

Conclusion Patients with TBI presenting with or without associated ECT present similar acute HPA response. AI is present in 23.6% of patients. Risk is increased in patients with low plasma ACTH levels and in patients with hemorrhagic shock. Both primary and secondary mechanisms of HPA failure were found. However, AI did not affect outcome.

Keywords Traumatic brain injury · Extracerebral trauma · Adrenal insufficiency · Cortisol · HPA axis · Adrenocorticotrophin hormone · Risk factors · Outcome

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Introduction

Disturbances of the hypothalamic–pituitary–adrenal (HPA) axis constitute a leading cause of neurophysiologic long-term sequelae after traumatic brain injury (TBI) [1]. Consensus guidelines focusing on the screening of these neuroendocrine disorders in TBI patients have been recently published [2]. The study of HPA axis disturbances in acute trauma patients has become a relevant clinical and scientific topic [3, 4], and recent studies support the existence of these disturbances in the acute phase after TBI [4–8], suggesting a relationship among HPA axis function with hemodynamic response [6, 7], immunomodulation [6], and outcome [8, 9]. Although mechanisms mediating these disturbances are not clear, both primary and secondary HPA failures have been suggested [6–8, 10].

In addition, TBI patients who are at high risk to develop adrenal impairment remain poorly determined, and its incidence presents a high variability depending on the definition we use [10]. Studies have shown contradictory results when reporting patients who are more likely to present adrenal impairment [4–14], and in most cases, the population of TBI patients studied was not homogeneous. Recent studies have also shown that HPA axis disturbances are common in trauma patients without TBI [15, 16]. The influence of extracerebral trauma (ECT) on the HPA response in the acute phase of TBI has not been extensively studied.

Therefore, we conducted a large prospective study in the acute phase after TBI aiming to evaluate HPA response in patients with TBI with and without associated extracerebral injuries, in an effort to investigate mechanisms underlying stress response in these patients.

Patients and Methods

Patients

We prospectively studied 165 consecutive patients with TBI admitted to the intensive care unit (ICU) in a tertiary hospital (Hospital Universitario Son Dureta, Palma de Mallorca, Spain) from November 2003 to September 2007.

We included patients with moderate or severe TBI who were sedated, intubated, and mechanically ventilated. Intracranial pressure (ICP) was monitored by an intraparenchymal probe (Camino®, Integra NeuroSciences, Plainsboro, NJ, USA) at neurosurgical team criteria.

Exclusion criteria were aged younger than 16 years, probability of survival less than 24 h, previous use of drugs known to affect cortisol secretion (corticosteroids, etomidate, ketoconazole), pregnancy and patients who had developed septic shock at the time of analysis. Patients treated with barbiturate coma at the time of analysis were also excluded [13].

Hospital research ethics committee approved the study and closest relative informed consent was obtained.

Management of ICP

Immediate removal of intracranial masses was performed at neurosurgical team criteria before ICU admission. Management of the patients with ICP monitoring was done according to a standard TBI protocol used in our ICU, as previously discussed [8, 13]. Briefly, sedation with midazolam and/or propofol and analgesia with morphine by continuous infusion i.v. Muscle paralysis to achieve better ventilation or to improve control of high ICP was induced with cisatracurium as required. Norepinephrine (NE) was administered to maintain cerebral pressure perfusion above 60 mmHg, when necessary. Treatment of ICP included control of general measures, mannitol, hypertonic saline and moderate hyperventilation according to jugular bulb oxygen saturation values. If second level measures were required to control high ICP, barbiturate coma, moderate hypothermia, decompressive craniectomy or placement of an external lumbar drainage were used according to the criteria of ICU and neurosurgical team.

Severity of Injury

Severity of injury at ICU admission was evaluated according to the Glasgow Coma Scale (GCS) score after resuscitation [17], the Injury Severity Score (ISS) [18], and the score of the Acute Physiology and Chronic Health Evaluation II (APACHE II) at initial 24 h after admission [19]. Patients were considered as having ECT if, in addition to brain injury, they presented a score of 3 or more in the abbreviated injury scale [20] in any of the following: face, chest, abdominal, pelvic, limbs. The existence of hemorrhagic shock also was indicative of ECT. Radiological degree of head injury was evaluated at ICU admission according to cranial computed tomography (CCT) scan features following TCDB classification [21].

Influence of Sedation

As some sedative agents have been suggested to affect HPA response [7, 13], we also studied the influence of sedation, analgesia, and muscle relaxation on the incidence of AI. Sedatives used within 24 h of collecting blood samples were recorded.

Samples and Analysis

Blood samples for plasma adrenocorticotrophin hormone (ACTH) and cortisol analysis were collected within 48 h of injury between 08:00 and 10:00 h. Blood samples were obtained through an arterial line. After baseline samples were drawn, a high-dose corticotrophin stimulation test (HDCST) was performed by injecting 250 μg of corticotrophin (Synacthene, Novartis, Switzerland). Blood samples were collected at 30 and 60 min afterwards. Whole blood was collected into EDTA crystal tubes with aprotinin to measure ACTH, and into crystal tubes without anticoagulant to measure cortisol. Samples were immediately centrifuged and kept cool at −70°C until measurement.

Plasma ACTH and serum cortisol were measured using an immunochemiluminescent assay: ACTH (Immulite 2000, DPC, Los Angeles, USA). Normal values: 9–52 pg/ml. The detection limit of the assay was 5 pg/ml. *Cortisol* (Advia, Centaour, Bayer, NY, USA). Normal values for non-stressed individuals in our laboratory are 4.30–24.40 μg/dl.

Definition of Posttraumatic Adrenal Insufficiency

The diagnosis of adrenal insufficiency (AI) in the acute phase in TBI patients remains controversial [10]. In our initial report in TBI patients [8], we used a cortisol response less than 9 μg/dl after the HDCST as a diagnostic tool. However, at the current moment we agree with other authors that baseline cortisol values must be included in the definition of posttraumatic AI [7, 10]. Therefore, we considered as diagnostic of AI the existence of baseline cortisol <5 μg/dl (7) or a delta cortisol after HDCST <9 μg/dl [8, 12].

Statistical Analysis

Results are presented as mean and the standard deviation (SD) or median and interquartile ranges (25th–75th) as appropriate. Comparison between groups was made using Student's *t*-test or Mann–Whitney test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. In order to examine the simultaneous effects of multiple variables on mortality, variables with a *P*-value < 0.15 in the univariate analysis were entered into a multivariate logistic regression analysis. Variables with a *P*-value > 0.10 were removed from the multivariate models according to a backward procedure. A two-tailed *P*-value < 0.05 was considered as the minimum level of statistical significance. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago).

Results

TBI patients with isolated brain injury and with associated ECT were comparable in baseline clinical characteristics, except in the radiological features (Table 1). As expected, a higher ISS was found in the group with associated ECT. ICP was monitored in 124 patients (75.1%). Extracerebral lesions were present in 57 patients, distributed as follows: 13 patients (7.9%) presented facial trauma, 43 patients (26.1%) with chest trauma, 21 patients (12.7%) with abdominal trauma, 20 patients (12.1%) with unstable pelvic trauma, 21 patients (12.7%) had significant limb injuries, and 14 patients (8.5%) suffered from hemorrhagic shock. Similar mortality rates were found in both groups (17.6% in isolated head injury vs. 14.0% in ECT patients, $P = 0.56$).

We found no major differences in the HPA response between patients with isolated TBI and with associated ECT (Table 2). A total of 39 patients (23.6%) fulfilled

Table 1 Clinical characteristics of TBI patients with and without ECT

	Isolated TBI ($n = 108$)	TBI + ECT ($n = 57$)	*P*-value
Age (years), median (24th–75th)	31 (19–48)	30 (22–48)	0.97
Female, *n* (%)	15 (13.9)	10 (17.5)	0.53
ISS, median (25th–75th)	18 (16–25)	25 (20–34)	<0.001
APACHE II, median (25th–75th)	16 (13–22)	19 (13–23)	0.12
GCS, median (25th–75th)	7 (5–9)	8 (6–11)	0.28
TCDB			<0.001
Type II	54	49	
Type III	15	2	
Type IV	3	0	
Evacuated mass	29	5	
Non-evacuated mass	7	1	
tSAH, *n* (%)	56 (51.9)	34 (59.6)	0.34
NE use, *n* (%)	57 (52.8)	28 (49.1)	0.66

ECT, extracerebral trauma; ISS, injury severity score; APACHE II, acute physiology and chronic health evaluation-II; GCS, Glasgow coma scale; TCDB, traumatic coma data bank; tSAH, traumatic subarachnoid hemorrhage; NE, norepinephrine

Table 2 HPA response in TBI patients with and without ECT

	Isolated TBI ($n = 108$)	TBI + ECT ($n = 57$)	*P*-value
ACTH (pg/ml)	11.7 ± 12.3	10.5 ± 11.4	0.12
ACTH < 9 pg/ml, *n* (%)	69 (63.9)	43 (75.4)	0.13
Baseline cortisol (μg/dl)	15.0 ± 9.0	15.6 ± 9.5	0.76
Cortisol basal < 5 μg/dl, *n* (%)	7 (6.5)	5 (8.8)	0.75
Δ Cortisol < 9 μg/dl, *n* (%)	14 (13.0)	13 (22.8)	0.10
Cortisol maximum (μg/dl)	31.8 ± 8.3	29.8 ± 8.2	0.13

ECT, extracerebral trauma; ACTH, adrenocorticotrophin hormone

criteria for AI (Table 2). Among them, 12/39 because of baseline cortisol levels <5 μg/dl, and 27/39 because of a delta cortisol <9 μg/dl. None of them fulfilled both criteria. The incidence of non-responders to the HDCST was higher in the ECT group (26 vs. 14%, $P = 0.10$) (Table 2).

All patients with low baseline cortisol presented with plasma ACTH <9 pg/ml (lower reference value), suggesting a central defect, whether in non-responders to the HDCST test, this fact was present in only 18.5% ($P < 0.001$). No differences were found regarding mortality or need of NE support between patients with and without AI (Table 3). Patients with and without AI differed in the plasma ACTH levels and in the incidence of hemorrhagic shock (Table 3).

We analyzed the use of the different sedatives, analgesics, and muscle relaxants in the 165 TBI patients stratified according to the presence or not of AI. No influence of these agents on HPA response was noted in these patients (Table 4).

Univariate analysis to predict mortality showed that variables with statistical significance were ISS, APACHE II, GCS, NE use, plasma ACTH, TCDB classification, and need of second level measures (Table 5). Logistic regression analysis showed that TCDB classification different than type II, ISS, plasma ACTH higher than 9 pg/ml, and need of second level measures to control ICP were independent predictors of death (Table 5).

Discussion

The results of our study suggest that TBI patients with and without ECT present similar HPA response. HPA impairment exists in one out of four TBI patients. Risk is increased in patients presenting with low plasma ACTH levels or hemorrhagic shock. Both primary and secondary mechanisms were found. Influence in outcome is unclear.

Table 3 Comparision analysis between patients with and without AI

	Baseline cortisol < 5 μg/dl ($n = 12$)	Δ Cortisol < 9 μg/dl ($n = 27$)	No AI ($n = 126$)	*P*-value
Age (years), median (25th–75th)	28 (18–35)	31 (19–48)	32 (22–49)	0.24
Female, *n* (%)	3 (25.0)	3 (11.1)	19 (15.1)	0.54
ISS, median (25th–75th)	18 (12–24)	20 (17–36)	18 (16–26)	0.37
APACHE II, median (25th–75th)	18 (15–20)	17 (12–25)	16 (13–22)	0.91
GCS, median (25th–75th)	7.5 (4–11)	7 (3–10)	7 (5–10)	0.78
TCDB, *n* (%)				0.14
Type II	7 (58.3)	14 (51.8)	82 (65.1)	
Type III	–	3 (11.1)	14 (11.1)	
Type IV	–	2 (7.4)	1 (0.8)	
Evacuated mass	5 (41.7)	5 (18.5)	24 (19.0)	
Non-evacuated mass	–	3 (11.1)	5 (4.0)	
tSAH, *n* (%)	5 (41.7)	14 (51.8)	71 (56.3)	0.59
Extracerebral trauma, *n* (%)	5 (41.7)	13 (48.1)	39 (31.0)	0.21
Hemorrhagic shock	2 (16.7)	5 (18.5)	7 (5.6)	0.08
ACTH < 9 pg/ml	12 (100)	5 (18.5)	95 (75.4)	<0.001
Second level measures	4 (33.3)	6 (22.2)	35 (27.8)	0.74
NE use	6 (50.0)	13 (48.1)	66 (52.4)	0.92
ICU mortality	1 (8.3)	7 (25.9)	19 (15.1)	0.30

ISS, injury severity score; APACHE II, acute physiology and chronic health evaluation-II; GCS, Glasgow coma scale; TCDB, traumatic coma data bank; tSAH, traumatic subarachnoid hemorrhage; ACTH, adrenocorticotrophin hormone; ICU, intensive care unit; NE, norepinephrine

Table 4 Sedatives, analgesics, and muscle relaxants use and relationship with AI

	Baseline cortisol < 5 μg/dl ($n = 12$)	Δ Cortisol < 9 μg/dl ($n = 27$)	No AI ($n = 126$)	*P*-value
Propofol, *n* (%)	12 (100%)	23 (85%)	110 (87%)	0.39
Midazolam, *n* (%)	7 (58%)	14 (52%)	66 (52%)	0.92
Morphine, *n* (%)	12 (100%)	23 (85%)	118 (93%)	0.18
Remifentanil, *n* (%)	0 (0%)	4 (15%)	8 (6%)	0.18
Cisatracurium, *n* (%)	5 (42%)	13 (48%)	38 (30%)	0.17
Haloperidol, *n* (%)	1 (8%)	3 (11%)	11 (9%)	0.92

Table 5 Univariate and multivariate analyses of factors associated with ICU mortality

	Univariate analysis			Multivariate analysis	
	Alive ($n = 138$)	Dead ($n = 27$)	*P*-value	Odds ratio (95% CI)	*P*-value
Age (years)	34 ± 16	44 ± 22	0.07		
ISS	20 ± 9	29 ± 12	0.004	1.09 (1.03–1.14)	0.001
APACHE II	17 ± 6	23 ± 7	<0.001	0.86 (0.73–1.01)	0.07
GCS	8 ± 3	6 ± 3	0.02	3.2 (1.1–9.2)	0.03
TCDB > II	44 (31.9)	18 (66.7)	0.001		
tSAH	72 (52.2)	18 (6.7)	0.17		
Extracerebral trauma	49 (35.5)	8 (29.6)	0.56		
NE use	64 (46.4)	21 (77.8)	0.003		
Second level measures	28 (20.3)	17 (63.0)	<0.001	5.0 (1.8–14.3)	0.002
ACTH> 9 pg/ml	37 (26.8)	16 (59.3)	0.001	4.4 (1.5–12.5)	0.006
Baseline cortisol < 5 μg/dl	11 (8.0)	1 (3.7)	0.69		
Δ Cortisol < 9 μg/dl	20 (14.5)	7 (25.9)	0.16		

Odds ratios shown for variables with $p < 0.10$. Results expressed as mean ± SD or *n* (%)

ISS, injury severity score; APACHE II, acute physiology and chronic health evaluation-II; GCS, Glasgow coma scale; TCDB > II, traumatic coma data bank classification different than type II; EM, evacuated mass; NEM, non-evacuated mass; tSAH, traumatic subarachnoid hemorrhage; ECT, extracerebral trauma; NE, norepinephrine

The study of the HPA response in the acute phase of trauma patients has become a relevant scientific topic [3–16]. Patients who are at the risk of presenting adrenal impairment are not well established, as incidence clearly varies according to the definition used [10], and, in addition, studies have shown different risk factors [4–9, 11–16]. Dimopoulou et al. [5] showed that endocrine disturbances in TBI patients were more likely to occur in older and more severely injured patients. An HPA blunted response was associated with hemodynamic instability and higher interleukin-6 levels [6]. Cohan et al. [7] documented a higher incidence of HPA impairment in patients who received etomidate, high doses of propofol, and barbiturates, and in patients with hypotension or with ischemic lesions. Llompart-Pou et al. [13] also showed a higher incidence of adrenal impairment in patients treated with barbiturate coma, and interestingly, in the group treated with barbiturates the existence of AI was associated with higher requirements of vasoactive support. Similar results were found in patients with hemorrhagic shock [12, 15], a finding that has been related to ischemia and necrosis phenomena of the adrenal gland [22]. Koiv et al. [11] found a relationship between basal cisterns dimensions and location of head injury with HPA response. Schneider et al. [23] found a high incidence of pituitary abnormalities in an imaging study in the acute phase of TBI. Contrary to these studies, other authors did not find any relation with different well-known prognostic factors in TBI patients, as age, Marshall score, APACHE II score, ISS [10] nor with the presence of focal lesions in CCT, GCS score [4], or ICP [5].

In this study, we compared acute HPA response in TBI patients presenting with and without ECT in order to determine the impact of systemic injury. Both groups had similar response, as previously found by Chiolero et al. [14], in a smaller group of patients. However, some differences were noted. The main difference was that patients with ECT presented a higher incidence of a blunted response to the HDCST.

Our large series of TBI patients identified AI in 23.6% of patients similar to previously reported when both baseline and stimulated cortisol values are taken into account [10]. Patients with TBI presenting with low plasma ACTH or hemorrhagic shock were more likely to develop posttraumatic AI.

Based on these findings, we speculate that posttraumatic AI has a double mechanism.

Hemorrhagic shock has been related with AI by Rushing et al. [15] and by Hoen et al. [12]. In the later study, the existence of AI, defined as a deficient response to the HDCST, was correlated with higher interleukin-6 levels and NE requirements. Probably, hemorrhagic shock existence explains the (non-significative, $P = 0.08$) higher incidence of a diminished adrenal reserve with normal ACTH levels detected in the ECT group, suggesting a primary adrenal failure. The second factor related to posttraumatic AI was the presence of low plasma ACTH levels, as all patients with low baseline cortisol levels had a plasma ACTH level below the normal reference value. This fact is quite important, as it suggests that posttraumatic AI, in this subset of patients with isolated TBI, is related to hypothalamus or pituitary failure rather than a primary failure, as previously reported by other authors [8]. Given the particular vascularization of the anterior lobe of the pituitary gland [24], this area appears especially vulnerable to traumatic injury and its consequences [11, 24], as confirmed in a imaging study by Schneider et al. [23].

In addition, we studied if sedatives use affected HPA response. In this large TBI population, we found no influence of these agents on stress response. These results

are contrary to those previously suggested, showing that adrenal response was affected by high-dose propofol [7] and barbiturate coma [7, 13]. Most of our patients received propofol at different doses, and none received barbiturates before performing the HDCST.

Treatment with low-dose steroids has become a common treatment in vasopressor-dependent septic shock patients [25]. Hypotension is one of the main causes of secondary insults and worst outcome in patients with TBI [26]. Several authors have supported a potential role of the treatment with low-dose steroids in patients with TBI to treat AI and improve hemodynamic status [3, 4, 6, 7, 10, 12, 13]. A small and retrospective study suggested that the hemodynamic response to hydrocortisone was correlated with an improved outcome in TBI [27]. However, patients who would benefit from this treatment have to be determined yet, and this point has to be considered crucial as recent evidence showed that treatment with high-dose methylprednisolone was detrimental after TBI [28]. Although certain consensus exists concerning the potential use of low-dose steroids to treat hemodynamic instability in determined subsets of TBI patients [3, 4, 6, 7, 10, 12, 13, 15], more controversial is the effect of AI in the final outcome. Moreover, in our prior report [8], we found that patients with isolated TBI presenting with low plasma ACTH had a favourable outcome compared with patients with normal ACTH levels, and we considered this fact as prognostic factor in TBI patients. This finding is also evident in the present study, along with other well-known prognostic factors in TBI. In addition, we found no differences in mortality or in NE use in AI group compared with non-AI group. Awaiting the results of a prospective study evaluating hydrocortisone use in TBI setting [7], and attending to our data and the increased mortality found in the CRASH trial [28], we would recommend considering treatment with low-dose steroids only in those TBI patients (with or without ECT) with most severe need of vasoactive therapy, as for example, those with hemorrhagic shock [12] or undergoing barbiturate coma [13].

Our study presents some limitations: AI has no clear definition in the TBI setting. Different test and criteria have been used and a consensus on its definition is warranted [6, 10]. We used the baseline cortisol level <5 μg/dl [7] and the blunted response after HDCST as previously performed in different studies [8, 12].

In conclusion, the results of our study suggest that TBI patients with and without ECT present similar HPA response, which is impaired in 23% of TBI patients. Risk is increased in patients presenting with low plasma ACTH levels or hemorrhagic shock by mediating primary and secondary mechanisms. However, in our study, the existence of AI did not affect outcome.

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Correlation between brain interstitial and total serum cortisol levels in traumatic brain injury. A preliminary study. Llompart-Pou JA, Pérez G, Pérez-Bárcena J, Brell M, Ibáñez J, Riesco M, Abadal JM, Homar J, Marsé P, Ibáñez, Burguera B, Raurich JM. **J Endocrinol Invest 2010; 33:368-72.**

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RAPID COMMUNICATION

Correlation between brain interstitial and total serum cortisol levels in traumatic brain injury. A preliminary study

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ABSTRACT. ***Introduction:*** **Brain cortisol availability has never been evaluated in patients with traumatic brain injury (TBI). Cerebral microdialysis is a well-established technique for monitoring brain metabolism in neurocritically ill patients, which may be used to measure interstitial cortisol. The objective of this preliminary study was to measure brain interstitial cortisol and its correlation with total serum cortisol in patients with TBI.** ***Methods:*** **We prospectively studied 6 patients with severe TBI admitted to the Intensive Care Unit of our tertiary University Hospital in which multimodal neuromonitoring including cerebral microdialysis with a high cut-off of 100 k-Da and 20-mm long membrane was used. Serum and brain interstitial cortisol microdialysis samples were obtained every 8 h and analyzed afterwards.** ***Results:*** **Linear regression analysis of total serum cortisol and brain interstitial cortisol in the whole population showed a moderate correlation (R^2=0.538, p<0.001, no.=118). However, intra-individual correlation showed a great variability, with correlation coefficients ranging from a R^2=0.091 to R^2=0.680.** ***Conclusion:*** **Our prospective and preliminary study showed a moderate correlation of brain interstitial cortisol and total serum cortisol values in patients with diffuse TBI. However, intra-individual analysis showed a great variability. These results suggest that total serum cortisol may not reflect brain cortisol availability in half of TBI patients.**

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INTRODUCTION

The study of the hypothalamic-pituitary-adrenal (HPA) axis response in the acute phase after traumatic brain injury (TBI) constitutes a relevant scientific topic (1-7). HPA response has been related with the severity of injury (1), outcome (2, 3), and hemodynamic instability in TBI patients (3-6). However, these studies have shown contradictory results (1-7). In addition, the biochemical diagnosis of HPA failure remains controversial, and its incidence depends on the definition and type of test used (8-10). Whether the evaluation of serum cortisol accurately reflects brain availability of cortisol has not been determined.

Cerebral microdialysis is a well-established technique for monitoring brain metabolism in neurocritically ill patients (11, 12). In addition to standard indications, microdialysis allows us to measure certain substances and metabolites in these patients, such as anti-epileptic drugs (13, 14) and antibiotics levels (15). Microdialysis techniques have been recently used to determine the relationship between interstitial cortisol with serum cortisol in different subsets of patients, as for example, obesity (16) and severe burns (17). However, a similar study in TBI patients has not been performed yet.

The objective of this preliminary study was to evaluate the feasibility of using cerebral microdialysis to estimate brain interstitial cortisol concentrations and to examine the correlation between total serum cortisol and brain interstitial cortisol in patients with TBI.

MATERIALS AND METHODS

This study was conducted at the Intensive Care Unit (ICU) of Son Dureta University Hospital (Palma de Mallorca, Spain). The Ethics Committee of the Balearic Islands approved the use of cerebral microdyalisis for investigational purposes on October 24th, 2007. In all cases, written informed consent for inclusion in the study was obtained from the closest relative. Serum and microdialysis samples were obtained in conjunction with a separate study investigating cytokines profile in patients with diffuse TBI (Dr Pérez-Bárcena, unpublished data).

Patient selection

We prospectively studied 6 patients with severe TBI admitted to the ICU. Patients between 18 and 65 yr with TBI and a diffuse lesion according to Marshall's classification (18) (classes II, III, and IV), who required intracranial pressure (ICP) and brain tissue oxygenation monitoring were eligible for the study. Patients with focal head injuries with a volume >25 ml and patients with coagulation or platelet count disturbances were not included.

In all patients, ICP was monitored using an intraparenchymal Camino catheter (Integra Neurosciences, Plainsboro, NJ, USA). The ICP catheter was placed in the frontal region of the most affected hemisphere diagnosed by cranial computed tomography. Brain tissue oxygenation was

Key-words: Brain interstitial cortisol, cerebral microdialysis, total serum cortisol, traumatic brain injury.

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also measured with a brain tissue oxygenation probe (Licox, Neurosciences) which was inserted through a double-lumen bolt in conjunction with the ICP catheter. Severity of injury was evaluated using the Glasgow coma scale after resuscitation (19). General management of all patients with severe TBI was standardized according to the Brain Trauma Foundation Guidelines (20), and has been summarized elsewhere (7). Briefly, sedation with midazolam and/or propofol and analgesia with morphine by continuous infusion iv. Muscle paralysis to achieve better ventilation or to improve control of high ICP was induced with cisatracurium as required. Norepinephrine (NE) was administered to maintain cerebral pressure perfusion (CPP) above 60 mmHg, when necessary. Treatment of ICP included control of general measures, mannitol, hypertonic saline and moderate hyperventilation according to jugular bulb oxygen saturation values. If second-level measures were required to control high ICP, barbiturate coma, moderate hypothermia, decompressive craniectomy or placement of an external lumbar drainage were used according to the criteria of ICU and neurosurgical team. Outcome was evaluated at ICU discharge using Glasgow outcome scale (21).

Microdialysis technique

Microdialysis catheters (CMA 71, CMA Microdialysis AB, Solna, Sweden) with a 100 k-Da cut-off and a 20-mm long membrane were inserted through a twist-drill accordingly to previous publications next to the double-lumen bolt for ICP and brain tissue oxygenation (22). The catheters were perfused with a central nervous system perfusion fluid (NaCl 147 mM, KCl 2.7 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 0.85 mM without dextran) at 0.3 µl per min. The vials were changed every 8 h to ensure enough amount of sample for analysis (between 80 and 140 µl). Microdialysis and serum blood samples were collected at the same time and stored at –80 C until analyzed. Microdialysis monitoring was started in all patients within 24 h after injury.

Cortisol analysis

Serum cortisol was analyzed using a immunochimioluminiscent assay (Cortisol ACS:Centaur. Siemens®) according to manufacturer's intructions. In this method, the cortisol sample (20 µl) competes with labeled cortisol with acridinium ester for binding with rabbit polyclonal antibody anticortisol of the solid phase. To analyze cortisol in microdialysis samples we used a modification of the technique described earlier using 75 µl of microdialysate. The method was calibrated with 13 different concentrations ranging from 0.07 µg/dl to 1.71 µg/dl of cortisol and adjusting the results to an exponential curve using a specific program (Microcal Origin 6.0). The coefficient of variation of this modified method was 9.1% and 8.6% for concentrations of 0.3 µg/dl and 1.0 µg/dl, respectively (no.= 10). The serum assay gave a coefficient of variation of 5.7%, 4.9%, and 5.1% for concentrations of 3.3 µg/dl, 21.4 µg/dl, and 35.8 µg/dl.

Statistical analysis

Variables are expressed in mean and SD. Correlation between total serum and microdialysis cortisol in the whole population and in intra-individual analysis was performed using linear regression. Data were analyzed using specific software: SPSS statistical package version 15.0 (SPSS Inc, Chicago).

Table 1 - *Baseline clinical characteristics and outcome of the 6 patients studied.*

	Gender	Age	GCS	Marshall	ICU GOS
Patient 1	Male	18	5	2	Severe disability
Patient 2	Female	18	6	3	Dead
Patient 3	Female	23	7	3	Moderate disability
Patient 4	Male	18	5	3	Dead
Patient 5	Male	30	5	2	Moderate disability
Patient 6	Male	54	8	2	Severe disability

GCS: Glasgow coma scale; Marshall: radiological classification of traumatic brain injuries according to Marshall's radiological classification of brain injury (18); ICU: intensive care unit; GOS: Glasgow outcome scale.

RESULTS

Baseline characteristics and outcome of the 6 patients studied are summarized in Table 1.

Mean total serum cortisol and brain interstitial cortisol were 15.9±9.2 and 1.1±1.0 µg/dl, respectively.

Linear regression analysis of total serum cortisol and brain interstitial cortisol (microdialysis samples) in the whole population showed a moderate correlation (R^2=0.538, p<0.001, no.=118) (Fig. 1). However, intra-individual correlation showed a great variability, with correlation coefficients ranging from a R^2=0.091 to R^2=0.680 (Fig. 2). Three out of 6 patients (50%) showed an extremely weak correlation (R^2<0.15), whereas the remaining 3 showed a moderate correlation (R^2>0.50) (Fig. 2).

DISCUSSION

To our knowledge, this is the first study reporting brain in-

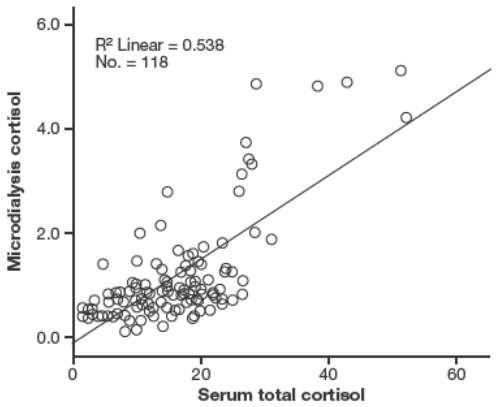

Fig. 1 - *Linear regression of the 118 samples obtained in the 6 patients. The concentration of cortisol is expressed in µg/dl. No.= number of paired samples.*

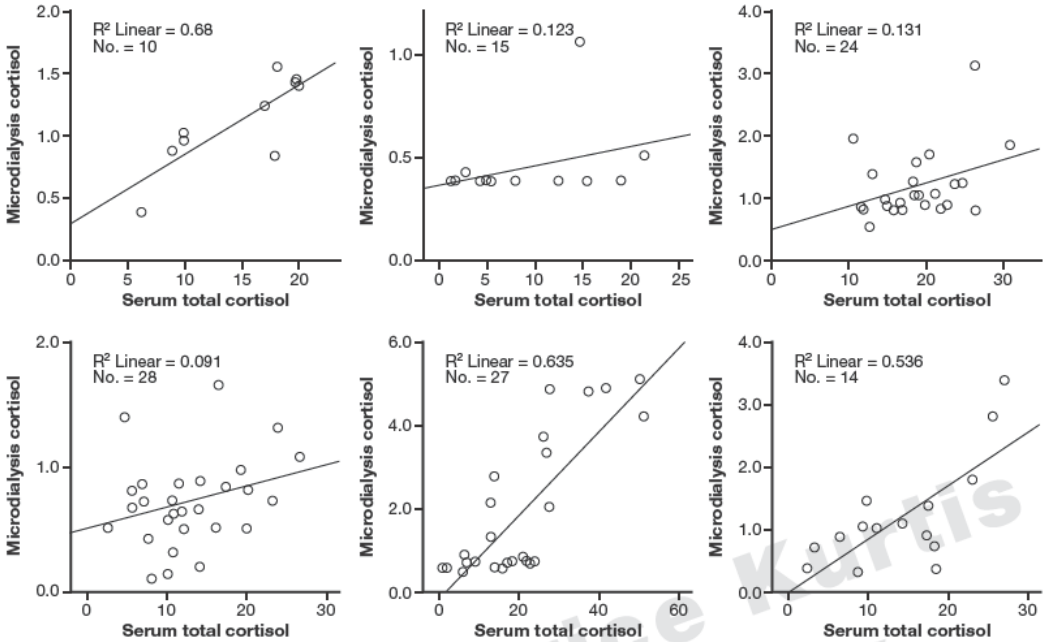

Fig. 2 - *Linear regression of the 6 patients individually analyzed. The concentration of cortisol is expressed in µg/dl. No.= number of paired samples.*

terstitial cortisol measurements in patients with traumatic brain injury. We demonstrated a moderate correlation of brain interstitial cortisol and total serum cortisol values. However, intra-individual analysis showed a marked variability.

Cortisol, the primary glucocorticoid, plays a major role in the maintenance of the homeostasis in the critically ill patient as a major component of the HPA response (23). Stimulation of the HPA axis from the hypothalamic paraventricular nucleus through complex and combined mechanisms causes secretion of glucocorticoids (cortisol), which act in both the brain and periphery to promote adaptation to stress (23). HPA disturbances are common in critically ill patients, and the TBI patients present specific characteristics, such as damage to the sella region (24), use of sedatives (3, 6), and presence of associated extracranial injuries (5, 7), which made the study of the HPA response even more complex. Different diagnostic criteria in this setting have resulted in a wide variability of incidence of HPA failure (8). In addition, most of these tests present important limitations in critically ill patients (25, 26). Whether total serum cortisol reflects what occurs in the brain has yet to be determined, as occurred with vancomycin (15) and phenytoin (13). Due to this circumstance we decided to carry out this preliminary study in TBI patients exploring cortisol levels in brain interstitial fluid and its correlation with total serum cortisol.

Our results showed an intra-individual lack of correlation of brain interstitial and total serum cortisol in half of the patients with diffuse TBI, raising the possibility that measuring total serum cortisol may not accurately reflect brain cortisol availability in all patients with TBI, in accordance with Cohen study in non-TBI critically ill patients (17). Our results using microdialysis technology are slightly higher to those reported by Cohen in burnt and non-burnt tissues (17). We underscore the lack of normal reference values in brain interstitial cortisol measurements, since this is the first study evaluating this topic.

Interstitial cortisol concentrations reflect the glucocorticoid pool available to pass through the cell membrane and bind to the glucocorticoid receptor (27), which is a crucial point in the maintenance of homeostasis. Cohen et al. showed a lack of correlation of total and free plasma cortisol with microdialysis measurements in burnt and non-burnt tissues, suggesting that plasma cortisol, in those critically ill patients, may not appropriately represent tissue cortisol actitvity (17), as seen in our study. These results suggest that tissue availability is influenced by some aspects different than serum cortisol values, such as interstitial fluid volume and capillary leakage (17). In addition, HPA response is closely linked to the cytokines production after TBI, and potentially could play a significant role in neuroinflammatory response (4). However, this issue has not been studied yet, and the number of patients in this preliminary study does not allow us to obtain conclusions about the potential relation of brain interstitial cortisol and mortality. In our series, the two

patients who died showed a similar profile than those who survived.

The potential influence of sedatives in microdialysis measurements has not been addressed in this study. Previously, different authors have addressed the influence of different agents, such as propofol (3), barbiturates (3, 6), etomidate (28), and midazolam (28) in serum cortisol measurements. This issue has not been evaluated in our study, but we must underscore that no patient received etomidate and, in addition, patients were managed according to a strict protocol to control intracranial pressure, so the potential effect of sedatives was minimized. To study brain interstitial cortisol dynamics and its relationship with ICP control and outcome in response to the administration of different sedatives agents seems, in our opinion, attractive.

Our study has some limitations: first, this is a limited sample size, although the total number of paired samples was high (no.=118). In addition, this technique is invasive in nature. Therefore, microdialysis should not be considered as a screening tool for HPA dysfunction in TBI patients. Second, as it is well-known that cortisol crosses the blood-brain barrier in patients with TBI and that it has a very low molecular weight (363 daltons), it is therefore likely that the recovery rate through the 100 kD microdialysis membrane catheter was high. However, we did not perform *in vitro* studies and the recovery rate has not been determined. Nevertheless in this study we evaluated the correlation between serum and brain interstitial cortisol values, rather than their absolute values. Third, this study was not designed to find a correlation of brain interstitial cortisol values with outcome. However, this way seems promising, opens a new field of study in the evaluation of HPA response in brain-injured patients, and therefore, should be considered as a working hypothesis for future studies. Interstitial cortisol measurements reflect brain tissue availability, so studying its response, in patients with severe TBI undergoing complete invasive neuromonitoring, may provide interesting information along with other established markers of metabolic cerebral damage, such as interstitial glucose, lactate, piruvate, lactate/piruvate ratio or glycerol, usually studied with microdialysis techniques.

In summary, in this preliminary study we showed a moderate correlation between brain interstitial cortisol and total serum cortisol values in patients with diffuse TBI. However, intra-individual analyses showed a great variability in the results, suggesting that total serum cortisol may not adequately reflect cortisol brain availability in half of these patients.

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ORIGINAL ARTICLE

Loss of Cortisol Circadian Rhythm in Patients with Traumatic Brain Injury: A Microdialysis Evaluation

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Abstract

Background Traumatic brain injury (TBI) is commonly associated with disturbances of the hypothalamic–pituitary–adrenal axis secretion. Cerebral microdialysis techniques have been recently applied to measure brain interstitial cortisol levels.

Methods We evaluated for the first time the circadian rhythm of cortisol secretion at 08:00, 16:00, and 24:00 h in the acute phase of TBI by determination of total serum and brain interstitial cortisol levels (microdialysis samples) in 10 patients with TBI. Non-parametric Friedman's two way analysis of variance test was used.

Results Mean age was 29.8 ± 13.6 years. Median Glasgow Coma Scale score after resuscitation was 5 (range 3–10). No differences were found in total serum ($P = 0.26$) and brain interstitial cortisol ($P = 0.77$) in the whole sample. Intraindividual analysis showed that circadian variability was lost in all patients, both in serum and brain interstitial cortisol samples in the acute phase after TBI.

Conclusion In our series, circadian variability of cortisol evaluated by serum and cerebral microdialysis samples seems to be lost in TBI patients.

Keywords Traumatic brain injury · Cortisol · Brain interstitial cortisol · Microdialysis · Circadian rhythm

Introduction

Hormonal secretion profile in healthy humans presents a typical circadian pattern which is mediated by the activation of the suprachiasmatic nuclei of the hypothalamus [1]. Cortisol is the major component of the host response to injury in critically ill patients [1]. Cortisol secretion is mediated by complex mechanisms resulting in a characteristic biphasic pattern with a peak between 06:00 and 08:00 a.m. and a through during the evening activity [1]. However, this circadian variability is usually lost in critically ill patients, especially in those with traumatic brain injury (TBI). Patients with TBI present specific characteristics, such as the direct injury to the hypothalamic–pituitary area [2], that difficults the study of the cortisol dynamics. A recent study in critically ill patients showed that circadian rhythm of cortisol secretion was only present in 37% of these patients, and this fact was even more pronounced in patients with brain injury [3].

Microdialysis techniques have recently allowed measuring interstitial cortisol in critically ill patients [4, 5]. A previous study in patients with diffuse TBI showed that

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brain interstitial cortisol presented a weak correlation with total serum cortisol in half of TBI patients evaluated [5], suggesting that serum cortisol may not reflect brain cortisol availability in most TBI patients.

The aim of the present study was to describe for the first time brain interstitial cortisol circadian pattern in patients with TBI.

Methods

The Ethics Committee of the Balearic Islands approved the use of cerebral microdialysis for investigational purposes on October 24th, 2007. In all cases, written informed consent for inclusion in the study was obtained from the patient's closest relative. The study was performed at the Intensive Care Unit (ICU) of Son Dureta University Hospital (Palma de Mallorca, Spain). Serum and microdialysis samples were obtained in conjunction with a separate study investigating cytokines profile in patients with TBI (Dr Pérez-Bárcena, unpublished data).

Patients

We prospectively studied 10 patients with severe TBI admitted to the ICU of our tertiary University Hospital. Patients between 18 and 65 years of age with a TBI and a diffuse lesion according to Marshall′s classification [6] (classes II, III, and IV), who required intracranial pressure (ICP) and brain tissue oxygenation monitoring, were eligible to participate in the study. Patients with coagulation or platelet disorders were not included.

In all patients, ICP was monitored using an intraparenchymal Camino catheter (Integra Neurosciences, Plainsboro, NJ, USA). Brain tissue oxygenation was measured with a brain tissue oxygenation probe (Licox, Neurosciences, Plainsboro, NJ, USA). Both catheters were inserted through a double-lumen bolt in conjunction in the frontal region of the most radiologically affected hemisphere in the cranial-computed tomography. General management of all patients with severe TBI was standardized according to the Brain Trauma Foundation Guidelines [7], and has been summarized elsewhere [5, 8]; briefly, sedation with midazolam and/or propofol and analgesia with morphine by continuous infusion iv. Muscle paralysis to achieve better ventilation or to improve control of high ICP was induced with cisatracurium as required. Norepinephrine (NE) was administered to maintain cerebral pressure perfusion (CPP) above 60 mmHg, when necessary. Treatment of ICP included control of general measures, mannitol, hypertonic saline, and moderate hyperventilation according to jugular bulb oxygen saturation values. If second level measures were required to control high ICP, barbiturate coma, moderate hypothermia, decompressive craniectomy, or placement of an external lumbar drainage were used according to the criteria of the ICU and neurosurgical team. No patient received steroids because of brain injury or other conditions during the study period. We documented the treatments received by all patients to control ICP as well as the infectious complications occurred. We evaluated the influence of radiological Marshall's classification [6] and outcome according to Glasgow Outcome Scale (GOS) [9] in the levels of cortisol.

Microdialysis Technique

Microdialysis catheters (CMA 71, CMA Microdialysis AB, Solna, Sweden) with a high-cut-off membrane of 100 kDa molecular weight and a membrane length of 20 mm were inserted by twist-drill craniotomy next to the double-lumen bolt for ICP and brain tissue O_2. Catheters were placed in a non-injured subcortical frontal region and were perfused with central nervous system perfusion fluid (NaCl 147 mM, KCl 2.7 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 0.85 mM without dextran) at 0.3 μl per minute. The vials were changed every 8 h (08:00, 16:00, 24:00) to ensure enough amount of sample for the analysis (between 80 and 140 μl). Microdialysis and serum blood samples were collected at the same time and stored at −80°C until analyzed. Microdialysis implementation was started within 24 h of TBI in all cases. Subsequent cranial-computed tomography showed adequate placement of microdialysis catheters. Since using the first sample retrieved after placement of the microdialysis catheter might introduce bias due to tissue damage by the surgical procedure, we excluded from the analysis the first sample obtained in all patients.

Cortisol Analysis

Serum cortisol was analyzed using an immunochemioluminiscent assay (Cortisol ACS:Centaur, Siemens®) according to manufacturer's instructions. In this method, the cortisol sample—20 μl—competes with labelled cortisol with acridinium ester for binding with rabbit polyclonal antibody anticortisol of the solid phase. To analyze cortisol in microdialysis samples we used a modification of the technique described earlier using 75 μl of microdialysate. The method was calibrated with 13 different concentrations ranging from 0.07 to 1.71 μg/dl of cortisol and adjusting the results to an exponential curve using a specific program

(Microcal Origin 6.0). The coefficient of variation of this modified method was 9.1 and 8.6% for concentrations of 0.3 and 1.0 μg/dl, respectively ($n = 10$). The serum assay gave a coefficient of variation of 5.7, 4.9, and 5.1% for concentrations of 3.3, 21.4, and 35.8 μg/dl.

Statistical Analysis

Variables are expressed in mean and standard deviation or numbers and percentages as appropriate. To evaluate daily circadian differences between cortisol levels in serum and

Table 1 Mean cortisol values in microdialysis and serum samples, intracranial pressure, brain tissue O_2 and cerebral perfusion pressure distributed by time of sampling

	Brain interstitial cortisol (μg/dl)	Total serum cortisol (μg/dl)	Intracranial pressure (mmHg)	Brain tissue O_2 (mmHg)	Cerebral perfusion pressure (mmHg)
Patient 1					
08:00	0.69 ± 0.12	14.43 ± 1.72	17.20 ± 5.63	34.60 ± 2.40	70.20 ± 5.13
16:00	0.64 ± 0.08	12.95 ± 1.88	15.17 ± 2.97	30.00 ± 3.98	66.33 ± 5.24
00:00	0.86 ± 0.12	11.98 ± 2.14	15.33 ± 1.05	34.50 ± 2.99	75.17 ± 7.16
Patient 2					
08:00	1.22 ± 0.40	22.24 ± 4.60	22.17 ± 2.61	28.17 ± 2.79	70.33 ± 5.13
16:00	2.22 ± 0.68	23.10 ± 5.15	25.33 ± 4.66	28.67 ± 5.53	70.67 ± 4.32
00:00	2.06 ± 0.66	20.65 ± 3.82	20.86 ± 1.96	25.29 ± 2.88	68.29 ± 3.40
Patient 3					
08:00	1.25 ± 0.27	20.23 ± 1.72	14.40 ± 2.54	29.80 ± 3.88	72.00 ± 3.64
16:00	1.03 ± 0.13	17.11 ± 1.89	14.17 ± 2.93	24.50 ± 1.80	72.50 ± 3.13
00:00	0.89 ± 0.15	19.32 ± 1.56	16.50 ± 2.94	27.83 ± 1.53	67.17 ± 2.20
Patient 4					
08:00	1.56 ± 0.31	15.95 ± 1.98	15.00 ± 3.03	31.25 ± 6.03	71.75 ± 6.86
16:00	1.13 ± 0.25	13.90 ± 2.30	17.50 ± 3.80	31.50 ± 3.28	73.00 ± 3.03
00:00	1.02 ± 0.13	15.12 ± 3.64	15.80 ± 1.24	28.60 ± 3.49	74.40 ± 2.30
Patient 5					
08:00	0.40 ± 0.10	9.25 ± 3.03	16.67 ± 1.36	16.83 ± 1.08	72.50 ± 3.87
16:00	0.56 ± 0.16	8.99 ± 2.60	19.71 ± 2.09	19.71 ± 2.39	74.86 ± 2.82
00:00	0.53 ± 0.13	6.42 ± 1.50	20.43 ± 2.36	19.86 ± 1.59	80.29 ± 4.71
Patient 6					
08:00	1.37 ± 0.46	14.95 ± 3.46	19.33 ± 2.76	24.17 ± 3.56	84.50 ± 5.61
16:00	0.86 ± 0.16	14.43 ± 3.42	17.83 ± 3.23	24.50 ± 2.01	83.17 ± 3.38
00:00	1.11 ± 0.44	14.62 ± 3.29	14.43 ± 2.25	25.43 ± 4.04	86.00 ± 6.49
Patient 7					
08:00	1.87 ± 0.97	17.08 ± 3.80	21.25 ± 3.14	19.25 ± 5.55	59.00 ± 4.38
16:00	2.42 ± 1.32	13.71 ± 2.52	18.50 ± 2.63	21.25 ± 3.64	59.50 ± 3.77
00:00	1.37 ± 0.48	16.10 ± 2.20	36.75 ± 7.50	21.50 ± .175	52.33 ± 3.28
Patient 8					
08:00	0.96 ± 0.12	14.40 ± 2.66	12.00 ± 1.61	18.17 ± 1.17	83.33 ± 6.31
16:00	1.09 ± 0.16	14.04 ± 2.76	12.86 ± 1.45	18.71 ± 1.47	84.43 ± 3.79
00:00	1.44 ± 0.45	11.35 ± 2.08	15.29 ± 1.71	20.57 ± 2.49	87.43 ± 3.95
Patient 9					
08:00	1.55 ± 0.23	19.53 ± 1.27	11.33 ± 3.49	25.40 ± 2.27	72.50 ± 4.64
16:00	1.32 ± 1.27	18.90 ± 3.39	8.83 ± 1.53	24.40 ± 2.56	77.67 ± 2.34
00:00	1.75 ± 0.41	16.73 ± 1.63	18.14 ± 2.70	20.33 ± 2.08	73.43 ± 4.79
Patient 10					
08:00	0.61 ± 0.31	11.69 ± 2.93	12.67 ± 1.43	27.33 ± 3.12	89.17 ± 5.48
16:00	0.92 ± 0.39	8.18 ± 2.13	12.17 ± 1.32	28.67 ± 3.70	84.00 ± 2.70
00:00	0.55 ± 0.26	10.06 ± 2.48	13.43 ± 1.44	28.14 ± 3.27	89.00 ± 3.61

microdialysis samples in the whole population and in every patient we used the non-parametric Friedman's two way analysis of variance test. To evaluate the influence of radiological classification and outcome in the cortisol levels we used the Mann–Whitney Test. A P value less than 0.05 was considered significant. Data were analyzed using specific software: SPSS statistical package version 15.0 (SPSS Inc., Chicago).

Results

We studied 10 patients with TBI. Eight were male (80%). Mean age was 29.8 ± 13.6 years. Median Glasgow Coma Scale score after resuscitation was 5 (range 3–10). Five patients (50%) presented a diffuse lesion type II, 4 patients (40%) a diffuse lesion type III and 1 patient (10%) presented diffuse lesion type IV. Three patients died in the ICU (GOS 1), 4 patients remained severely disabled (GOS 3) and 3 patients had moderate disability (GOS 4).

Mean total serum and brain interstitial cortisol levels, mean ICP, mean brain tissue O_2, and mean cerebral perfusion pressure in all patients are detailed in Table 1. Using Friedman's two way analysis of variance test for serum and brain interstitial samples, we observed an absence of circadian variability in the whole sample for total serum ($P = 0.26$) and brain interstitial cortisol ($P = 0.77$), as well as in intraindividual analysis. In addition, we found that both serum and brain interstitial cortisol presented an initial peak followed by a progressive decline. Brain interstitial and total serum cortisol levels in the 5 days within TBI are shown in Fig. 1 distributed by 8 h-frames. To evaluate the potential influence of infections and treatments used to control ICP in cortisol values, we describe the treatments received by each patient in Table 2. Mean total serum and brain interstitial cortisol levels according to Marshall classification and GOS are shown in Fig. 2.

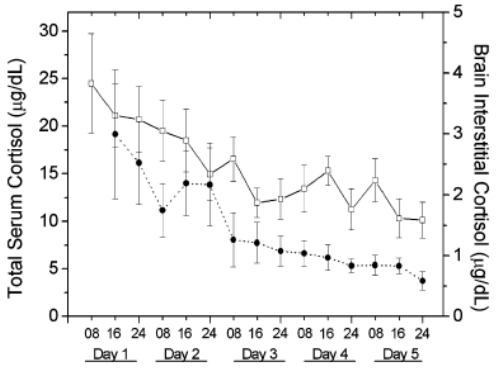

Fig. 1 Mean values of total serum cortisol and brain interstitial cortisol through days 1–5 after TBI. Cortisol values are expressed in µg/dl. *Squares*: total serum cortisol. *Circles*: brain interstitial cortisol

Discussion

Our study demonstrates that hypothalamic–pituitary–adrenal axis circadian rhythm seems to be disrupted in patients with TBI, evaluated by brain interstitial and total serum cortisol levels analysis.

Measuring interstitial cortisol constitutes a novel approach to the study of the hypothalamic–pituitary–adrenal axis, since it reflects the glucocorticoid pool available to pass through the cell membrane and bind to the glucocorticoid receptor, a keypoint in the maintenance of homeostasis [10]. Some groups have used microdialysis technique in burnt [4] and TBI [5] patients in a preliminary form, suggesting that total serum cortisol may not appropriately reflect the cortisol tissue availability [4, 5].

Our study evaluates for the first time the brain interstitial cortisol pattern in patients with severe TBI. Our results showing an altered circadian rhythm both in brain interstitial and serum samples are in agreement with previous studies evaluating cortisol secretion profile in blood samples in patients with TBI. These studies used different diagnostic criteria which influenced their results. Paul and Lemmer [3] showed that circadian rhythm of cortisol was present only in 37% of critically ill patients, being their results more marked in patients with craniocerebral injuries. Savaridas et al. [11] observed a diurnal variation of cortisol in 8 out of 15 neurocritically ill patients with subarachnoid hemorrhage or TBI. Cohan et al. [12] observed that diurnal variation of cortisol was lost in patients with TBI and extracerebral trauma, similarly as Woolf et al. [13] had reported. The study by Schwarz et al. [14] in patients with ischemic stroke determining cortisol in the same time frames used in our study found no significant differences in adrenocorticotropin hormone or cortisol levels. Our results using total serum and brain interstitial cortisol showed that diurnal variation was lost in 100% of TBI patients.

Although in this study we found that both total serum and brain interstitial cortisol circadian rhythm were disturbed in a similar form, our previous study suggested that serum and brain interstitial cortisol may not be correlated in half of TBI patients, suggesting a possible dissociation between serum and interstitial cortisol circadian patterns. This fact raises the possibility that the disruption of the blood–brain barrier (BBB), which has been observed in experimental and human TBI [15], might influence the detection of cortisol in these patients. However, it is well

Table 2 Summary of infections occurred and treatments received to control intracranial pressure during cortisol evaluation

	Infection	Osmotic agents	Barbiturate coma	Moderate hypothermia	Decompressive craniectomy	Lumbar drainage
Patient 1	No	Yes	No	Yes	No	No
Patient 2	No	Yes	Yes	Yes	No	No
Patient 3	Yes	Yes	No	No	No	No
Patient 4	Yes	Yes	Yes	Yes	No	No
Patient 5	No	Yes	Yes	Yes	No	No
Patient 6	No	Yes	No	No	No	No
Patient 7	No	Yes	Yes	Yes	No	No
Patient 8	No	No	No	No	No	No
Patient 9	No	Yes	Yes	Yes	Yes	No
Patient 10	No	No	No	No	No	No

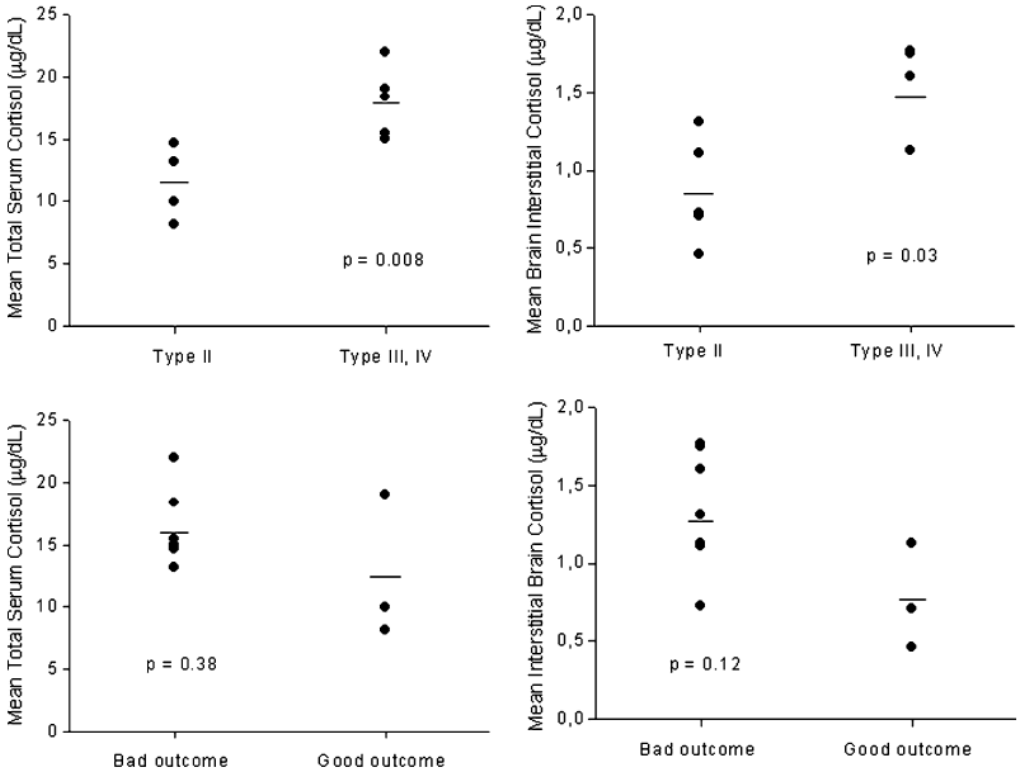

Fig. 2 Bivariate scattergrams of total serum cortisol and brain interstitial cortisol concentrations expressed as mean values for each patient plotted against Marshall classification (Type II—5 patients vs. Type III and IV—5 patients) and GOS (good outcome—3 patients vs. bad outcome—7 patients). *Good outcome*: complete recovery and moderate disability. *Bad outcome*: death, vegetative state and severe disability

known that in patients with TBI, cortisol crosses the BBB, and consequence of its very low molecular weight (363 Da), it is likely that its recovery rate through the 100 kDa microdialysis membrane catheter would be high. We did not perform in vitro studies and the recovery rate has not been determined. Therefore, such assumption cannot be extracted from these preliminary results.

We observed that patients with worst radiological injuries (Type III and IV in Marshall's classification) presented higher cortisol values compared with patients classified as Type II. No relationship was found with GOS. This fact is intriguing, and warrants further studies. However, we would prefer to interpret this information with caution, since the small number of patients studied implies that spurious associations could not be avoided. Therefore, we believe that our study is not designed to confirm this association.

Our study presents some limitations: first, the number of patients studied is rather small. Second, microdialysis samples reflect mean cortisol in samples in an 8-h time frame, not at a single time point. Third, since the bedside CMA analyzer is not available in our centre, we cannot correlate our results with conventional microdialysis measurements, such as lactate, pyruvate, glucose, etc. Lastly, for obvious concerns, reference brain interstitial levels in healthy volunteers are lacking. Therefore, we believe that these results should be considered with caution but constitute a basis for the development of future studies.

In conclusion, we describe for the first time the brain interstitial cortisol profile in patients with TBI. We found that circadian cortisol rhythm is abolished in TBI, as shown by microdialysis and serum determination. The study of the cortisol circadian rhythm in TBI patients warrants further analysis.

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5. Recapitulación

Esta tesis doctoral resume nuestros estudios en la evaluación del eje HHS en el paciente crítico. La enfermedad crítica en cualquiera de sus manifestaciones, representa un estrés de gran intensidad y persistente en el tiempo para los pacientes. De un modo general, el tratamiento debe encaminarse al reconocimiento del agente agresor y a la rápida restauración de los mecanismos fisiopatológicos afectados, con especial atención al sistema cardiovascular (Messotten, 2008). En muchos casos, el fallo del sistema cardiovascular está mediado por la disfunción del eje HHS, y es bien conocido que el cortisol representa un papel fundamental en la respuesta de la adaptación al estrés (Annane, 1998; Marik, 2002; Cooper, 2003). El objetivo de esta tesis ha sido caracterizar la respuesta del eje HHS en los pacientes críticos, evaluar el impacto de la LDST y finalmente investigar el papel de la microdiálisis cerebral en el estudio del eje HHS y sus potenciales aplicaciones futuras.

Desde el estudio de Annane y cols (Annane, 2002), el tratamiento con LDST se implantó de modo generalizado en los pacientes sépticos y en los pacientes no sépticos con hipotensión arterial de causa no justificada en la mayoría de UCIs de nuestro entorno. En nuestros estudios incluyendo pacientes con shock séptico, comprobamos que el tratamiento con LDST no supuso una mejoría en términos de mortalidad ni una disminución del tiempo de shock tras ajustar los grupos por gravedad. Comprobamos además que la mortalidad se correlacionó con la edad, puntuación en la escala SOFA y con el recibir tratamiento antibiótico empírico inadecuado, factores pronósticos habituales en los estudios de pacientes en shock séptico (Vincent, 2006; Garnacho Montero, 2003).

Además, comprobamos que las dosis de soporte vasoactivo con Noradrenalina fueron las mismas tras 24 horas de haber recibido o no tratamiento con LDST, independientemente de las cifras de cortisol basal y la respuesta al HDCST, y observamos que ningún parámetro bioquímico de función suprarrenal (cortisol basal o tras estimulación suprarrenal con HDCST) se asociaba a una mejor respuesta hemodinámica a los corticoides. Estos resultados nos llevaron a modificar nuestra práctica habitual en este grupo de pacientes, de modo que, en la actualidad, sólo tratamos con LDST los casos más graves (aquellos que precisan soporte con Noradrenalina a dosis superiores a 1 µg/kg/min) y además, no seguimos de modo excluyente los resultados del HDCST. Deben considerase también los potenciales efectos secundarios del tratamiento con corticoides (Britt, 2006; Beale, 2010). Esta actitud ha sido refrendada por el estudio CORTICUS (Sprung, 2008), publicado unos meses más tarde que nuestro primer trabajo (Raurich, 2007) y que mostró, en pacientes menos graves que el estudio de Annane et al (Annane, 2002), que el tratamiento con LDST no aportaba beneficios en términos de mortalidad y que los pacientes tratados con LDST presentaban una mayor incidencia de hiperglucemia, hipernatremia y nuevos episodios de shock séptico. Posteriormente, las recomendaciones actualizadas de la *Surviving Sepsis Campaign* (Dellinger, 2008) recomendaron también un uso más restrictivo de la LDST.

El siguiente paso en nuestra investigación, y que supuso un mayor grado de dificultad, fue el estudio del eje HHS en el paciente con TCE, puesto que debe considerarse la especial anatomía y vascularización del área hipotálamo-hipofisaria, que puede haberse visto dañada de modo directo o indirecto. No

existe ningún estudio prospectivo que demuestre un beneficio de la LDST en este grupo de pacientes, por lo que pensamos que primero debía caracterizarse la disfunción del eje HHS, los factores de riesgo asociados y la relación con el pronóstico.

Los principales resultados de nuestro estudio, que incluyó 165 pacientes con TCE, mostraron una incidencia de disfunción del eje HHS del 23.6% (39/165 pacientes), que no se vio marcadamente influenciada por la existencia de traumatismo extracraneal. Empleamos como criterios diagnósticos de insuficiencia suprarrenal la existencia de un cortisol basal < 5 μg/dL o una respuesta a la estimulación glandular mediante HDCST ≤ 9 μg/dL. La incidencia observada es acorde con la documentada previamente empleando definiciones similares (Bernard, 2006). Por otra parte, la ausencia de diferencias marcadas entre los pacientes con y sin traumatismo extracraneal asociado ya fue documentada en una muestra mucho más reducida de pacientes (Chiolero, 1988). Sin embargo debe reseñarse un matiz. Los pacientes con TCE puro cumplieron el criterio diagnóstico determinado por un cortisol basal < 5 μg/dl y todos ellos presentaron una buena respuesta al HDCST, mientras que los pacientes con traumatismo extracraneal cumplieron criterios de ISR fundamentalmente por una mala respuesta a la HDCST.

No se halló relación entre ISR y el pronóstico, siendo los factores de riesgo asociados una baja estimulación hipofisaria (ACTH ≤ 9 pg/mL) y la existencia de shock hemorrágico. Estos datos abren un debate interesante puesto que en nuestro anterior estudio incluído en esta tesis, que incluyó 50 pacientes con TCE puro que recibieron un manejo clínico homogéneo, aquellos que presentaron niveles de ACTH plasmática ≤ 9 pg/mL durante las primeras 48

horas de ingreso en UCI, presentaron una menor mortalidad (Odds ratio 22.37). Sólo un 7% de los pacientes con ACTH ≤ 9 pg/mL fallecieron y además lo hicieron por causas extracraneales, mientras que la mortalidad entre los pacientes con ACTH > 9 pg/mL alcanzó el 55%, la mayoría de ellos debido a hipertensión intracraneal refractaria. Otros autores (Barton, 1987; Koiv, 1997), en la línea de este resultado, mostraron que los pacientes con sobreactivación del eje HHS en la fase precoz postraumática presentaban una mayor mortalidad. Por otra parte, la relación entre el shock hemorrágico y la existencia de ISR en el paciente traumático ha sido previamente sugerida, y está mediada fundamentalmente por fenómenos de isquemia y necrosis glandular (Hoen, 2002; Rushing, 2006). Los factores asociados con un aumento de la mortalidad en nuestros estudios fueron una puntuación más elevada en los diferentes índices de gravedad empleados, la necesidad de utilizar medidas de segundo nivel para el tratamiento de la hipertensión intracraneal y la existencia de niveles de ACTH plasmática > 9 pg/mL. No hallamos relación con la presencia de ISR.

Evaluamos además la influencia de los distintos sedantes empleados sobre el desarrollo de ISR. Contrariamente a los hallazgos de otros autores, no hallamos relación entre el uso de dosis menores de propofol, midazolam, morfina, remifentanilo, cisatracurio y haloperidol con el desarrollo de ISR en los pacientes con TCE. Otros estudios hallaron relación con el uso de dosis muy elevadas de propofol (Cohan, 2005), barbitúricos (Cohan, 2005; Llompart-Pou, 2007, ***Anexo 1***) y etomidato (Vinclair, 2008), pero en nuestro estudio los pacientes que habían recibido etomidato o coma barbitúrico fueron excluídos. Con estos resultados, consideramos no indicado evaluar el tratamiento con

LDST como respuesta al estrés en pacientes con TCE e inestabilidad hemodinámica, como era nuestra intención inicial. Sólo en aquellos subgrupos de pacientes tratados con coma barbitúrico o con la presencia de shock hemorrágico intercurrente podría valorarse el tratamiento con LDST en la fase aguda del TCE.

Llegados a este punto, en el que nuestros estudios clínicos mostraron resultados que no apoyan el uso de LDST en pacientes sépticos ni traumáticos, decidimos volver atrás y tratar de analizar los mecanismos implicados en la respuesta del eje HHS ante una situación de estrés. Empleando técnicas de microdiálisis cerebral, que permiten la obtención de muestras de microdializado en el intersticio cerebral, fuimos el primer grupo en determinar las concentraciones de cortisol en dicho espacio y su patrón temporal en pacientes con TCE. Volviendo a la figura 2, vemos como el cortisol en el intersticio refleja el *pool* disponible para la célula, fundamental en el mantenimiento de la homeostasis y la respuesta al estrés (Cohen, 2009). En unas muestras reducidas (n=6 y n=10), observamos que en la mitad de pacientes con TCE el cortisol sérico total no refleja adecuadamente el cortisol intersticial cerebral, y que el ritmo circadiano de la secreción de cortisol se encuentra abolido tanto en suero como en el intersticio cerebral. Otros autores mostraron que la secreción de cortisol en diferentes poblaciones de pacientes neurocríticos no mostraba un patrón normal en suero (Woolf, 1990; Schwarz, 2003, Savaridas, 2004; Cohan, 2005; Paul, 2007). Nuestros resultados abren un nuevo campo de estudio en la evaluación del eje HHS en el paciente con TCE. Aunque es evidente que nuestros estudios con microdiálisis cerebral no tienen aplicación clínica

inmediata, pensamos que abren una nueva vía de investigación a este nivel y que permitirá la creación de nuevas hipótesis de trabajo en el futuro. Resulta atractivo pensar en que diferentes tratamientos o sedantes empleados puedan modificar la disponibilidad de cortisol a nivel del intersticio cerebral y con ello influir en la respuesta inflamatoria local. El conocer y poder modular la respuesta inflamatoria local podría ayudar a entender los mecanismos fisiopatológicos implicados en el desarrollo del edema cerebral postraumático. Además, debe investigarse el papel potencial de las cifras de cortisol cerebral como factor pronóstico, junto a otros marcadores de estrés metabólico habitualmente empleados en los estudios con microdiálisis, como la glucosa, el lactato, la relación lactato/piruvato y el glicerol (Bellander, 2004). El estudio de las cifras de cortisol cerebral podría responder el por qué los pacientes con TCE y ACTH plasmática disminuída al ingreso en nuestro anterior estudio (Llompart-Pou, 2007) presentaron un mejor pronóstico. Sin embargo, el limitado número de pacientes estudiados, el carecer de valores de normalidad en población sana y el no haber realizado estudios *in vitro* previos, hacen que consideremos esta línea de investigación como preliminar.

En resumen, esta tesis no apoya el llamado tratamiento sustitutivo suprarrenal con LDST en los pacientes críticos, salvo en situaciones especiales. La introducción de las técnicas de microdiálisis a nivel cerebral para el estudio de la respuesta del eje HHS ante el estrés, empleadas por vez primera en este trabajo, abre una nueva línea de investigación en el estudio de la disponibilidad de cortisol a nivel tisular.

6. Conclusiones

Las conclusiones de este trabajo son las siguientes:

-En nuestra población no seleccionada de pacientes en shock séptico, el tratamiento con dosis bajas de corticoides no se asoció a una mejoría de la mortalidad, a una disminución del tiempo de shock ni tampoco a una disminución de los requerimientos de soporte vasoactivo a las 24 horas del tratamiento, independientemente de las cifras de cortisol basal y de la respuesta a la estimulación glandular con HDCST.

-Los pacientes con TCE con una menor activación del eje HHS definido por unos niveles disminuídos de ACTH plasmática (≤ 9 pg/mL) al ingreso en la UCI presentan una mortalidad menor. La incidencia de disfunción suprarrenal en el TCE es del 23%, sin hallarse relación con el resultado final de estos pacientes, ni con la existencia de traumatismo extracraneal o los sedantes utilizados.

-La microdiálisis cerebral constituye un método novedoso empleado por primera vez en el estudio de las cifras de cortisol en el intersticio cerebral. Su análisis muestra que el cortisol sérico total puede no representar la disponibilidad cerebral de cortisol en la mitad de los pacientes con TCE y que el ritmo circadiano del cortisol se encuentra abolido en todos los pacientes con TCE tanto a nivel sérico como en el intersticio cerebral. Estos resultados podrían tener impacto futuro en el estudio del edema cerebral postraumático.

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8. Anexo

Llompart-Pou JA, Pérez-Bárcena J, Raurich JM, Burguera B, Ayestarán JI, Abadal JM, Homar J, Ibáñez J. Effect of barbiturate coma on adrenal response in patients with traumatic brain injury. **J Endocrinol Invest 2007**; **30:393-8.**

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Effect of barbiturate coma on adrenal response in patients with traumatic brain injury

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ABSTRACT. ***Introduction:*** **Barbiturate coma is the second tier measure recommended by guidelines to treat post-traumatic refractory intracranial pressure. Systemic hypotension is its most important side effect. Recent evidence suggests that low-dose corticosteroid therapy may be used in a subset of patients with traumatic brain injury (TBI) to avoid hypotension. We evaluated adrenal function in TBI patients undergoing barbiturate coma, as treatment of their refractory intracranial hypertension.** ***Materials and methods:*** **We prospectively studied 40 patients with moderate to severe TBI. Group A (17 patients) were treated with barbiturate coma. Group B (23 patients) presented intracranial hypertension controlled with first tier measures, and acted as a control. Adrenal function was evaluated by using the high-dose corticotropin stimulation test within 24 h after brain injury and after barbiturate coma induction.** ***Results:*** **Within 24 h after TBI, adrenal function was similar in both groups. Once barbiturate coma was induced, patients in group A treated with barbiturate coma presented a higher incidence of adrenal insufficiency compared with the control group B (53% *vs* 22%, p=0.03). Patients treated with barbiturates, who developed adrenal impairment, required higher doses of norepinephrine to maintain cerebral perfusion pressure than patients treated with barbiturates without adrenal impairment (1.07±1.04 μg/kg/min *vs* 0.31±0.32 μg/kg/min, p=0.03).** ***Conclusions:*** **Patients with TBI treated with barbiturate coma are at higher risk of developing adrenal insufficiency. This subset of patients presented higher requirements of vasoactive support to avoid hypotension. In these patients corticosteroid therapy may have potential therapeutic implications to treat hemodynamic instability.**

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INTRODUCTION

Barbiturate coma is the recommended therapy to control refractory intracranial hypertension (ICH) in patients with traumatic brain injury (TBI). The Brain Trauma Foundation Guidelines support its use in this situation, with an evidence level class II (1). Its use to control post-traumatic refractory ICH ranges from 13 to 56% (2-5). A high incidence of neuroendocrine disturbances in patients with TBI has been recently demonstrated (6), and the study of the hypothalamic-pituitary-adrenal (HPA) axis in TBI patients has become a scientific topic of major interest. Consensus Guidelines on screening of pituitary disturbances to reduce long-term sequellae after TBI have been published recently (7). Although there is some controversy in the literature, several recent reports have found a significant relationship between HPA response in the early phase after TBI and outcome (8, 9). The HPA response appears to be impaired when barbiturates are used (8), a circumstance also described in recent animal studies, which suggest that the suppression of HPA axis occurs if high doses of barbiturates are administered (10). The aim of our work was to prospectively study the effect of barbiturate coma on HPA axis response, in TBI patients with refractory ICH.

Key-words: Traumatic brain injury, barbiturate coma, adrenal insufficiency, hypotension, corticosteroids

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MATERIALS AND METHODS

Patients and management

We prospectively studied 40 patients with moderate to severe TBI admitted to the Intensive Care Unit (ICU) of a third level Univer-

sity Hospital (Hospital Universitario Son Dureta), from September 2003 to March 2005. Seventeen patients developed ICH refractory to first tier measures and were treated with barbiturate coma (group A). As a control group, we studied 23 patients with moderate to severe TBI admitted in the ICU who developed ICH controlled with first tier measures (group B). The Hospital Research and Ethics Committee gave its approval and informed consent was obtained from closest relatives. Exclusion criteria were age lower than 16 yr, pregnancy, patients who had developed septic shock and previous use of drugs known to affect cortisol secretion (etomidate, steroids).

Patients were managed according to a standardized TBI protocol used in our ICU to control intracranial pressure (ICP) as previously described (9). All patients were sedated with midazolam and/or propofol by continuous iv infusion and analgesia was accomplished with morphine. All patients were intubated and mechanically ventilated. In order to achieve better ventilation or to improve control of high ICP, muscle paralysis with cisatracurium was induced as required. Norepinephrine (NE) was administered to maintain cerebral pressure perfusion (CPP) above 60 mmHg, when necessary. Treatment of ICP included control of general measures, mannitol, hypertonic saline and moderate hyperventilation according to jugular bulb oxygen saturation values. When ICP became refractory with first tier measures, barbiturate coma with thiopental or pentobarbital was induced according to a previously published protocol (5). Daily electroencephalogram (EEG) was performed and burst suppression pattern was the objective, as previously defined (5).

ICP was considered refractory if the following criteria were present in the absence of external manoeuvres (2, 5):

1) ICP between 20-29 mmHg for 30 min, or
2) ICP between 30-39 mmHg for 15 min, or
3) ICP higher than 40 mmHg for at least 1 min.

ICP was measured by an intraparenchymal probe (Camino®, Integra NeuroSciences, Plainsboro N.J. USA) zeroed at Monroe's foramen. Severity of injury at admission was evaluated according to the Glasgow coma scale (GCS) score after resuscitation (11) and the injury severity score (ISS) (12). The degree of head injury was graded radiologically by ICU admission cranial computed tomography (CCT) scan according to Marshall's classification (13).

Samples and analysis

All patients included in this study were initially assessed for adrenal insufficiency within 24 h after the brain injury between 08:00 and 10:00 h. After baseline samples were drawn, a high-dose corticotrophin stimulation test (HDCST) was performed by injecting 250 µg of corticotrophin iv. Blood samples were collected at 30 and 60 min after the corticotrophin injection. To facilitate a better understanding we considered this test an ' early study". After barbiturate coma was induced and a EEG-burst suppression pattern was obtained (24-36 h after initiating barbiturate therapy), we performed a second HDCST. We established days 5-6 after injury as adequate time to perform the second HDCST in the control group, as in our experience most patients need barbiturate therapy to control ICP after several days of TBI. All patients in this control group remained sedated and mechanically ventilated at that time. This second HDCST was considered as the "late study".

All samples were obtained through an arterial line. The diagnosis of relative adrenal gland insufficiency was established when the highest cortisol response at 30 or 60 min after HDCST was less than 9 µg/dl (8). Baseline cortisol less than 4 µg/dl was considered indicative of absolute adrenal insufficiency, in agreement with previous reports which considered severe adrenal insufficiency when baseline cortisol levels were less than 4 µg/dl (14) or 5 µg/dl (8).

Analysis

Whole blood was collected into EDTA crystal tubes with aprotinin to measure ACTH and into crystal tubes without anticoagulant to measure cortisol. Samples were immediately centrifuged and kept cool until measurement. If ACTH analysis was not done the same day samples were stored at –80 C.

Plasma ACTH and serum cortisol were measured using an immunochemiluminescent assay: ACTH (Immulite 2000, DPC Los Angeles, USA). Normal values: 9-52 pg/ml. The detection limit of the assay was 5 pg/ml. Cortisol (Advia Centaour, Bayer, NY, USA). Normal values for non-stressed individuals: 4.30-24.40 µg/dl.

Statistical analysis

Data were expressed as mean and SD or median and interquartiles 25th -75th as appropriate. Continuous data were compared using Mann-Whitney U Test. Fisher's exact test was used to compare categorical data. A p-value <0.05 was considered significant. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 11.0 (SPSS Inc, Chicago, USA).

RESULTS

We studied 40 patients with moderate to severe TBI. They were classified according to the Marshall scale as follows: 0 patients had a diffuse lesion type I, 16 patients had a diffuse lesion II, 7 patients had a diffuse lesion III, 1 patient had a diffuse lesion IV, 12 underwent craniotomy to evacuate a focal mass, and 4 patients had a non-evacuated mass >25 ml. We found no differences in both groups regarding radiological features. Groups A and B were also comparable in age, sex, GCS and ISS (Table 1).

In the early phase, both groups presented similar plasma ACTH and baseline levels, as well as stimulated cortisol at 24 h after TBI (Table 2). In the late study, baseline and stimulated cortisol values were lower in group A than in control group B, reaching statistical significance (Table 2).

Patients in group A had a higher incidence of adrenal insufficiency than patients in group B (53% *vs* 22%, p=0.05), made up of a higher incidence of absolute adrenal insufficiency (18% *vs* 0%, p=0.03) and a trend to a higher incidence of relative adrenal insufficiency in the late study (41% *vs* 22%, p=0.30) (Table 3). It must be underlined that 94% of patients (16 out of 17) in group A received NE to maintain normal values of blood pressure levels and CPP, compared with 39% (9 out of 23) in group B (p<0.001) (Table 3).

When we analyzed the 17 patients in group A we found no association with mortality evaluated at ICU discharge, in patients who developed adrenal insufficiency and patients who did not (55% *vs* 50%,

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Table 1 - *Clinical characteristics of groups treated with or without barbiturates. Data are shown as median and interquartiles 25th -75th unless noted.*

	Group A (barbiturates) No =17	Group B (control) No =23	p
Age (yr)	35 (22-62)	27 (19-52)	0 50
Sex (male/female) n	16/1	20/3	0 62
GCS	7 (3-10)	7 (5-8)	0 74
ISS	25 (18-35)	20 (17-27)	0 22
Day of study	5 (4-6)	6 (5-6)	0 32
Mortality, n (%)	9 (53%)	1 (4%)	0 001

GCS: Glasgow coma scale; ISS: injury severity score; Day of study: day after traumatic brain injury

Table 2 - *Plasma ACTH and baseline and stimulated cortisol values in both groups. Results are shown in mean±SD. Early: studies performed within 24 h after traumatic brain injury. Late: studies performed when patients underwent barbiturate coma (group A) or control determination (group B).*

	Group A (barbiturates) No =17	Group B (control) No =23	p
ACTH (pg/ml)			
early	23.3±28 3	21 5±50 0	0 09
late	13 2±9 4	17 1±21 1	0 69
Baseline cortisol (µg/dl)			
early			
late	18 0±9 8	15 1±9 4	0 39
	14 5±8 8	20 6±7 3	0 02
Cortisol 30 min (µg/dl)			
early	27 9±7 6	27.9±8.8	0.80
late	24 9±9 0	34 8±10 2	0 004
Cortisol 60 min (µg/dl)			
early	30 6±6 6	31 3±9.1	0.94
late	25 7±9 0	37 6±10 1	0 001

p=0 82). However, the presence of adrenal impairment in group A was correlated with a higher requirement of NE doses (1 07±1 04 µg/kg/min *vs* 0.31±0 32 µg/kg/min, p=0 03) to maintain CPP at pre-determined levels. We also compared the incidence of adrenal insufficiency in patients treated with thiopental (no =10) and pentobarbital (no =7). A trend to a higher incidence of adrenal insufficiency was found

Table 3 - *Number (%) of patients in both groups presenting adrenal impairment. Early: studies performed within 24 h after traumatic brain injury. Late: values when patients underwent barbiturate coma (group A) or control determination (group B).*

	Group A no =17	Group B no =23	p
Absolute adrenal insufficiency early, no (%)	0 (0%)	2 (9%)	0 50
late, no. (%)	3 (18%)	0 (0%)	0 03
Relative adrenal insufficiency early, no (%)	4 (23%)	4 (17%)	0 70
late, no (%)	7 (41%)	5 (22%)	0 30
Global adrenal insufficiency early, no (%)	4 (23%)	6 (26%)	1.0
late, no (%)	9 (53%)	5 (22%)	0 05
Norepinephrine late, no (%)	16 (94%)	9 (39%)	0 001

in patients treated with pentobarbital than in those treated with thiopental (71% *vs* 40%, p=0.20).
The main results of the study are summarized in Table 4.

DISCUSSION

The results of our study suggest that patients with TBI who present refractory ICH treated with barbiturate coma are at an increased risk of developing adrenal impairment.
The possibility of developing hypopituitarism after TBI constitutes an increasingly recognized pathology (15, 16). Consensus guidelines on screening of these endocrine abnormalities in mid- and long-term post-TBI have been recently published (7, 16). However, the study of these patients in the acute phase remains controversial. The association between HPA axis response and outcome after TBI has been recently studied with contradictory findings (6, 8, 9, 14). A good understanding of the hormonal changes occurring after TBI is challenging, because of the complexity of its different components and its modulation by different hormones and cytokines (15, 17). In addition, several tests and criteria have been used in these reports (8, 9, 15, 18). A recent study proposes the 60 min response after HDCST as the best method to evaluate adrenal gland function in acute TBI patients. This study reviews the variable incidence of adrenal insufficiency that can be detected, depending on the different diagnostic criteria used (19).
Barbiturates have a well-known neuroprotector effect accomplished through different mechanisms. The most significant may be related to coupling of cerebral blood flow to regional metabolic demands, with subsequent beneficial effects on ICP and global cerebral perfusion (1, 2, 5, 20). Near maximal reductions in cerebral metabolism and cerebral blood flow occur when EEG burst suppression is induced (1).
Studies concerning influence of barbiturates in adrenal axis in humans are limited. Recently, therapy with barbiturates has been suggested to play a role in post-traumatic adrenal insufficiency (8). In a study which evaluated adrenocortical function in critically ill patients 24 h after a single dose of thiopental, the incidence of adrenocortical insufficiency evaluated by cortisol increment after HDCST was 29% (21). This suppressive effect has been suggested to be more likely to occur when high doses of barbiturates are used in animal models (10). A previous study in dogs anesthetized with thiopental showed that cortisol response to ACTH was significantly decreased when compared to control animals (22). Barbiturates have been suggested to affect adrenal response by mediating two different mechanisms:
- increasing corticosteroid metabolism inducing liver P450 cytochrome enzyme system (23, 24) and
- inhibiting steroidogenesis by interacting with the neurotransmitter γ-aminobutyric acid (GABA) receptor (25)

In our study, we found that a significant percentage of the patients studied under barbiturate therapy presented adrenal insufficiency. The need to use NE to maintain CPP over 60 mmHg was higher in the group of patients treated with barbiturates than in the control group, as could be expected. The most important finding in those patients treated with barbiturates who developed adrenal impairment was their higher requirements of NE therapy, compared to those patients treated with barbiturates, who presented a normal adrenal response.
These findings raise an important question. A well-known and most frequent side effect of barbiturate coma therapy is systemic hypotension (1, 2, 5, 20). The incidence of hypotension when barbiturate coma was used was higher than 60%, depending on the definition used (2, 5). Hypotension is one of the main causes of secondary insults and the worst outcome in patients with TBI (26). Hypotension is also one of the main clinical features of adrenal failure; treatment with low doses of steroids has been associated with an important improvement in hemodynamic status and decreased mortality in patients with septic shock (27). Barbiturate-induced hypo-

Table 4 - *Main results of the study, summmarizing the incidence of adrenal insufficiency in patients treated or not with barbiturates and the vasopressor requirements in barbiturate-treated patients presenting with or without adrenal insufficiency.*

Adrenal insufficiency	
Barbiturate group 53%	Control group 22%
Vasopressor requirements in barbiturate group	
With adrenal insufficiency	Without adrenal insufficiency
1.07±1.04 μg/kg/min	0.31±0.32 μg/kg/min

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tension is mediated by a reduction of peripheral resistances and cardiac index (19). Corticosteroids are known to enhance myocardial contractility and vascular smooth tone, in response to adrenergic stimuli, by increasing adrenoreceptor sensitivity to catecholamines (28).

Several authors have previously supported a possible role of low-dose corticosteroid therapy in TBI patients (8, 19). The subsets of TBI patients who would benefit from steroid therapy in the early phase has yet to be determined (19). Considering the higher incidence of systemic hypotension in TBI patients treated with barbiturate coma (2, 5), we postulate that TBI patients undergoing barbiturate therapy would benefit from low-dose corticosteroid therapy to avoid barbiturate-associated hemodynamic instability. This therapy may result in a decrease in secondary ischemic insults.

The use of low-dose steroids could be extrapolated to other subsets of TBI patients. However, it must be considered that a multicenter randomized trial evaluating the effects of high-dose methylprednisolone in TBI patients demonstrated a higher mortality and disability in patients treated with methylprednisolone compared with placebo (29). However, the doses and the anti-inflammatory effects of methylprednisolone and low-dose hydrocortisone are not comparable.

We must acknowledge the limitations of this study. First, this is a small sample size of TBI patients who underwent therapeutic barbiturate coma. In addition, it was difficult to find an adequate TBI population of control cases because ICH was refractory and had to be actively treated. We decided to compare patients with refractory ICH treated with barbiturates with patients with ICH controlled with first tier measures, so we cannot definitively exclude a potential role of the worsening of the ICH itself, in the adrenal response impairment. However patients in both groups were initially comparable in several well-known prognosis factors, such as age, GCS score and ISS.

Secondly, we did not measure corticosteroid binding globulin levels, which are known to decrease during the acute phase of brain injury (30), and the calculated free cortisol index could not be obtained and correlated with total serum cortisol. However, the use of calculated free cortisol is a standard measurement in daily clinical practice (8) since the measurement of corticosteroid binding globulin is not available in many laboratories.

Thirdly, we performed a single HDCST within 24 h of TBI and after initiating barbiturate coma. Other authors have performed serial determinations of baseline cortisol to evaluate adrenocortical function (8) and also adrenal reserve has been studied by low-dose corticotropin stimulation test, which appears to be more sensitive in non-critically ill patients (6, 31). However, its use when evaluating critically ill patients has been recently criticized (32) because the low-dose test induces supramaximal stimulation of the adrenal glands for only 30 min and may not appropriately evaluate the capacity of the adrenal glands to maintain maximal cortisol production in response to a major ongoing stress, as shown in a recent study including TBI patients (19).

In conclusion, TBI patients who develop refractory ICH treated with barbiturate coma risk developing adrenal insufficiency and associated hemodynamic instability. The use of a low-dose steroid therapy may have potentially important therapeutic implications in the treatment of hemodynamic status in these patients. Ongoing studies will help to further elucidate this question.

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