MEMORIA DE TESIS DOCTORAL

Utilidad de los agonistas α-2 en la prevención de la taquiarritmia en el postoperatorio de cirugía cardíaca pediátrica

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A la Margarita, en Pau, en Max i en Teo;

als meus pares, en Josep i la Conxita i

a en Vicente i la Joana.

ÍNDICE

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1.1. CARDIOPATÍAS CONGÉNITAS

Las cardiopatías congénitas son las malformaciones congénitas más frecuentes. Su incidencia se sitúa entre el 6 y el 12 por 1000 recién nacidos vivos.

En base a los resultados presentados por el *Grup de Treball en Cardiopaties Congènites del Programa Director de la Malaltia Cardiovascular* en el *pla d'atenció de les cardiopaties congènites a Catalunya*, publicado en mayo de 2008, se calcula que en Cataluña viven unas 9.700 personas afectas de cardiopatía congénita de menos de 16 años. En la actualidad, el 85% de los recién nacidos vivos afectos de una cardiopatía congénita alcanzan la edad adulta. A pesar de los avances técnicos y de manejo clínico y farmacológico alcanzados en las tres últimas décadas, la cirugía de la cardiopatía congénita en la edad pediátrica conlleva una morbilidad y mortalidad elevadas. La mortalidad global de los pacientes sometidos a cirugía de cardiopatía congénita se sitúa alrededor del 5-6% y en determinados grupos de pacientes con criterios de complejidad quirúrgica elevada esta mortalidad supera el 50 %(1).

1.2. ARRITMIAS Y CIRUGÍA DE CARDIOPATÍA CONGÉNITA

La arritmia cardiaca es una de las complicaciones más graves en el postoperatorio inmediato de cirugía de cardiopatía congénita, con una incidencia que se sitúa entre el 27-48%y una mortalidad que puede alcanzar el 12%(2).

Las arritmias postoperatorias pueden clasificarse en dos grandes grupos. Las bradiarritmias y las taquiarritmias.

Las bradiarritmias incluyen la disfunción del nodo sinusal y el bloqueo auriculoventricular. El bloqueo (AV) completo adquirido postoperatorio tiene una incidencia que oscila entre el tres y el seis por cien; es más frecuente en cirugías que afectan al tracto de salida del ventrículo izquierdo, septo interventricular y especialmente en la cirugía correctora de la tetralogía de Fallot y de la transposición de grandes vasos. Las bradiarritmias son, muchas veces (66%) autolimitadas y, fácilmente tratables temporalmente en el postoperatorio inmediato con la utilización del marcapasos secuencial. La persistencia de bloqueo AV completo después de dos semanas del postoperatorio constituye una indicación de implantación de marcapasos definitivo.

Las taquiarritmias son las arritmias más frecuentes en el postoperatorio inmediato. La etiología de las taquiarritmias en el contexto del postoperatorio cardiaco es multifactorial con la participación de factores intraoperatorios y extraoperatorios. Las opciones terapéuticas son, a día de hoy, todavía limitadas y, en las últimas tres décadas se han producido pocos avances en el manejo y prevención de éstas (3,4).

Las taquiarritmias se clasifican en función de: 1) el mecanismo etiopatogénico causante de la arritmia y 2) su localización.

1) en función de su etiopatogenia dividiremos las taquiarritmias en dos grandes grupos (figura 1):

1.a) taquiarritmias por reentrada y
1.b) taquiarritmias automáticas.

La clasificación etiopatogénica entre arritmias automáticas y por reentrada resulta de especial interés desde el punto de vista clínico en la unidad de cuidados intensivos puesto que tiene importantes implicaciones terapéuticas. Las taquiarritmias por reentrada son las arritmias más frecuentes en el periodo neonatal y se trata de las arritmias menos frecuentes en el postoperatorio inmediato. Son arritmias que aparecen y revierten de forma súbita con un fenómeno descrito típicamente como de interruptor "*on-off*". Presentan frecuencias cardíacas fijas y se trata de arritmias que típicamente responden a la cardioversión farmacológica y a la cardioversión eléctrica. Las taquiarritmias automáticas en cambio, son las arritmias más frecuentes en el postoperatorio inmediato. Aparecen de forma progresiva y revierten lentamente con un fenómeno típico de calentamiento "*warm-up*" y enfriamiento "*cool-down*" progresivo (Figura 1) . Son arritmias refractarias al tratamiento farmacológico y no responden, de forma característica, a la cardioversión eléctrica (5,6)

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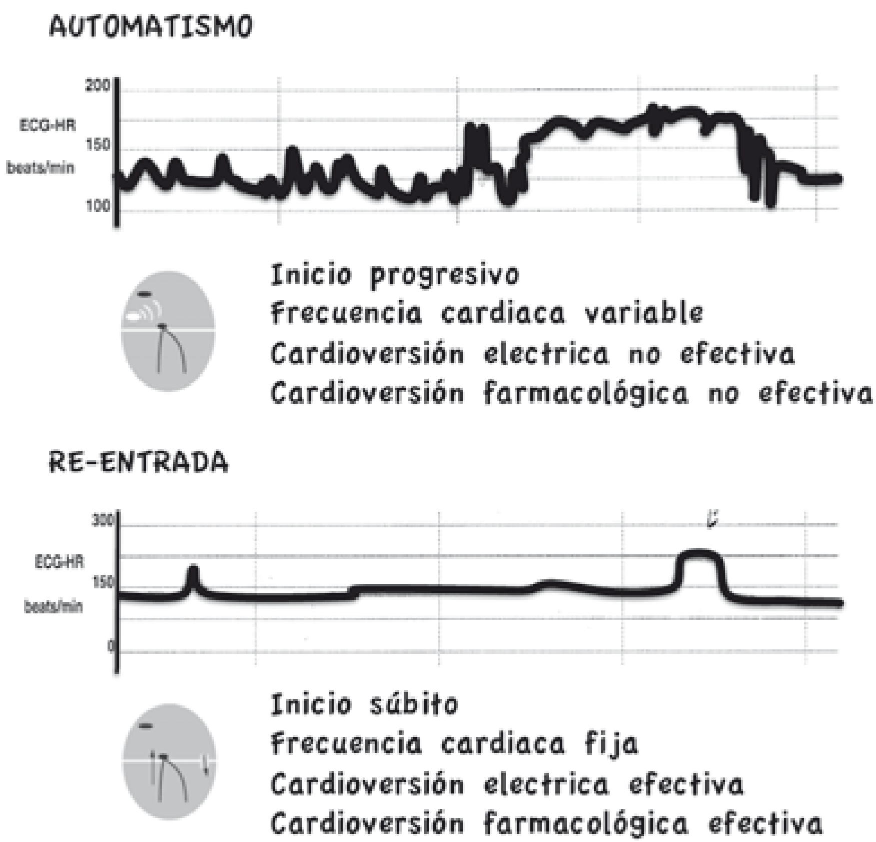

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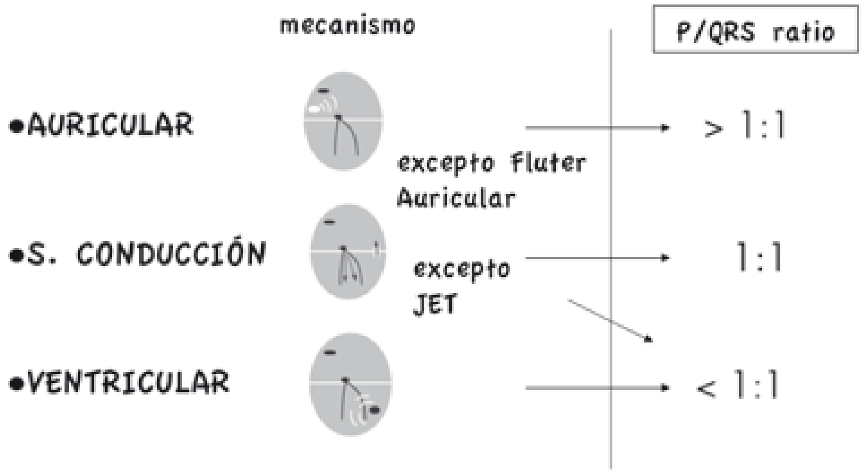
mecanismo
P/QRS ratio
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•S. CONDUCCIÓN
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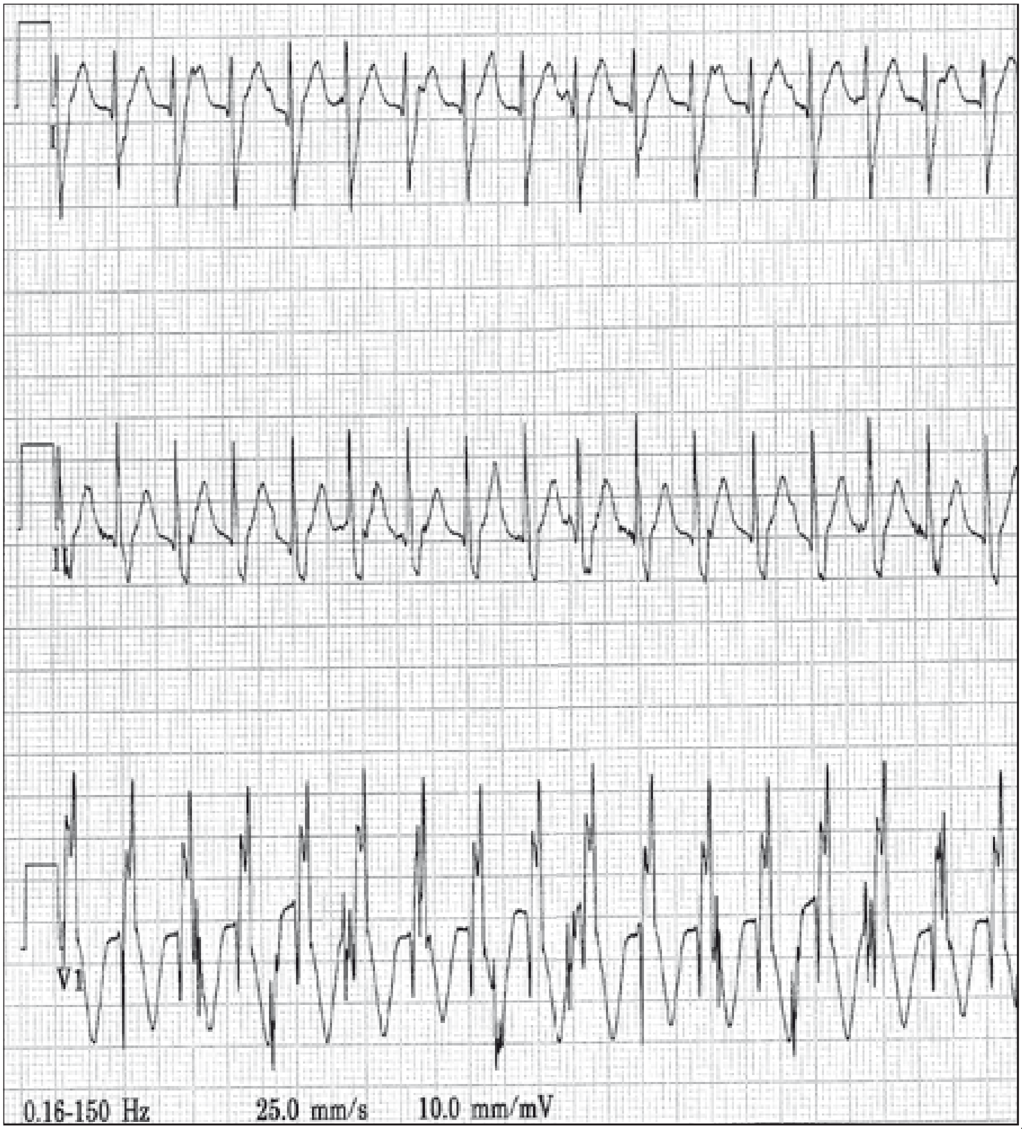

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Entre los factores asociados a la aparición de JET se encuentran: 1) la edad (más frecuente en neonatos y lactantes), 2) intervenciones con scores de complejidad elevados y con tiempos quirúrgicos prolongados, siendo particularmente frecuente en cirugía correctiva de canal auriculoventricular y en cirugía neonatal de corrección de transposición de grandes vasos y 3) en postoperatorios que requieren dosis elevadas de soporte inotrópico. En los análisis multivariantes de las distintas series publicadas, la utilización de dosis elevadas de inotrópicos, tiempos de circulación extracorpórea prolongados y la presencia de signos analíticos de isquemia miocárdica se asocian de forma constante a la aparición de JET(8–10). Estos datos sugieren que la existencia de descarga adrenérgica ya sea exógena (secundaria a fármacos inotrópicos o vasoactivos) o endógena (respuesta sistémica al stress quirúrgico) junto a otros factores asociados al propio acto quirúrgico, puede tener una importante participación en la aparición de esta arritmia en el postoperatorio de cirugía cardiaca. Así pues, la activación del sistema simpático y la liberación masiva de catecolaminas plasmáticas, consecuencia de la respuesta al estrés quirúrgico, podrían tener un papel clave en la etiopatogenia de la taquiarritmia postquirúrgica(11,12). En este sentido, la modulación de la respuesta simpática en el perioperatorio de cirugía de cardiopatía congénita podría ser beneficiosa para la restauración de la función orgánica(13). Disminuir la activación de esta cascada inflamatoria en el postoperatorio inmediato permitiría disminuir la morbilidad asociada, disminuyendo el número de arritmias, mejorando la función cardiaca y disminuyendo los días de ventilación mecánica y los días de hospitalización. Una de las estrategias utilizadas tradicionalmente en cirugía cardíaca para bloquear la respuesta al estrés quirúrgico es la

utilización de altas dosis de opioides durante la cirugía lo que conlleva un aumento en los días de ventilación mecánica y de la estancia media en las unidades de cuidados intensivos(14). Recientemente, algunos estudios sugieren los beneficios de los agentes agonistas α-2 adrenérgicos en el perioperatorio de cirugía cardíaca(15). La utilización de agonistas α-2 bloquea la respuesta simpática catecolaminérgica pudiendo así atenuar la disfunción hemodinámica perioperatoria minimizando las complicaciones cardiacas asociadas a la cirugía de la cardiopatía congénita y, en concreto, la incidencia de arritmia.

1.3. DEXMEDETOMIDINA

I.3.1 Introducción

Dexmedetomidina (DXM) es un agonista α-2 selectivo, S-enantiomero de medetomidine, un producto utilizado en medicina veterinaria como sedante y analgésico desde hace muchos años. Dexmedetomidina tiene propiedades sedantes, analgésicas y ansiolíticas. A diferencia de otros sedantes y analgésicos como benzodiacepinas, barbitúricos y opioides, produce menos depresión respiratoria lo que lo hace un fármaco atractivo para el manejo de la sedación y analgesia en unidades de cuidados intensivos(16).

1.3.2. Marco histórico

El principio activo de dexmedetomidina es propiedad de *Orion's pharmaceutical R&D*. Las autoridades reguladoras europeas no permitieron la introducción del medicamento *Dexdor*®, nombre con el que *Orion's pharmaceutical R&D* pensaba comercializar dexmedetomidina en Europa en los años 90 y esta cedió los derechos de distribución del fármaco a la multinacional farmacéutica *Hospira* quien la comercializó fuera de Europa con el nombre de *Precedex*®. En 1999 la *U.S Food and Drug Administration* (FDA) aprobó el uso de dexmedetomidina para la sedación de pacientes adultos intubados dentro de las unidades de cuidados intensivos y, posteriormente, en el año 2008, para la sedación de procedimientos médicos o quirúrgicos realizados fuera de la UCI sin necesidad de intubación. En la actualidad *Precedex*® está disponible en más de 30 países fuera de Europa

incluyendo EEUU desde el año 1999 y Japón desde el año 2004. En septiembre de 2011 la Agencia Europea del medicamento autorizó la comercialización del medicamento *Dexdor*® por procedimiento centralizado indicado para la sedación de pacientes adultos en unidades de cuidados intensivos. La indicación terapéutica aprobada en ficha Técnica es la siguiente: "…para la sedación de pacientes adultos en unidades de cuidados intensivos que requieran un nivel de sedación no más profundo que despertarse en respuesta a la estimulación verbal (correspondiente a un grado de 0 a 3 en la Escala de Sedación y Agitación de Richmond (RASS))." Esta autorización cubre a los 27 países de la Unión Europea y, en el momento de la redacción de este documento *Dexdor*® ya está disponible en Alemania, Austria, Dinamarca, Suecia, Finlandia, Inglaterra y España. En España *Dexdor*® esta comercializado desde febrero de 2013.

1.3.3. Propiedades Bioquímicas.

El hidroclorato de dexmedetomidina es un S-enantiomero de medetomidina y, químicamente se presenta como: (+)-4-(S)–[1-(2,3-dimetilfenil) etil]-1H-Imidazol monoclorito (figura 4). La dexmedetomidina tiene un peso molecular de 236,7 daltons. El rango de pH oscila entre 4,5 – 7. Es soluble en agua, tiene un pK_a de 7.1 y no contiene propilenglicol o lípidos. Su coeficiente de partición octano:agua a pH 7.4 es 2.89.

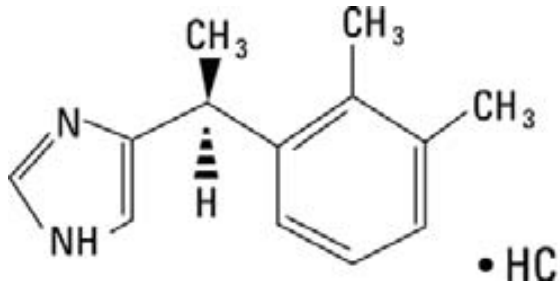

Figura 4. Estructura química de la dexmedetomidina

1.3.4. Dexmedetomidina y los receptores α-2 adrenérgicos

Dexmedetomidina ejerce su acción a través de los receptores α-2 adrenérgicos. Los receptores α2 se clasifican en tres grupos: imidazoles, phenylethylaminas y oxalozepinas. Dexmedetomidina, al igual que la clonidina, es miembro del grupo de los imidazoles que tienen una elevada ratio de especificidad sobre los receptores α2 respecto a los α1. Dexmedetomidina tiene una ratio de especificidad α2:α1 más elevada (1600:1) que la de la clonidina (200:1).

El efecto más conocido de los α-2 adrenérgicos a nivel cerebral es la inhibición presináptica de la liberación de noradrenalina(17)(18). No obstante, estos receptores suponen una pequeña proporción del total de receptores α-2 y la mayoría de efectos clínicos de la dexmedetomidina están mediados por la activación de los tres subtipos de receptores postsinápticos (α-2A, α-2B y α-2 C). Cada uno de estos subtipos es responsable único de algunas de las acciones de los α-2 (Figura 5). El subtipo A, el predominante a nivel de sistema nervioso central, es responsable de los efectos sedantes, analgésicos y del efecto simpaticolítico; el subtipo B, mayoritariamente localizado en la vasculatura periférica, es responsable de la respuesta hipertensiva

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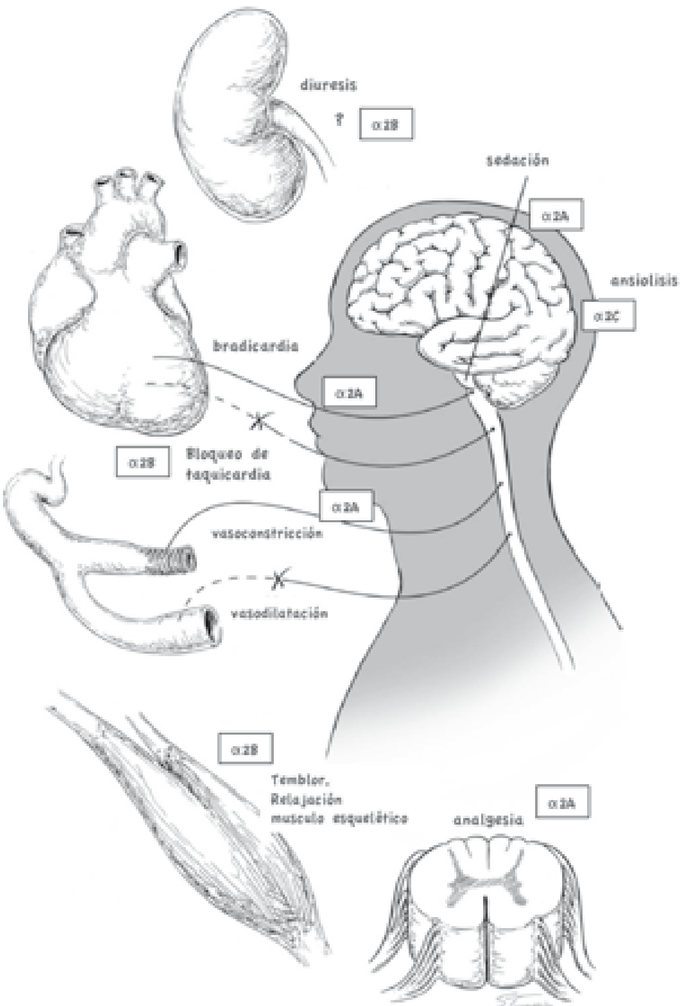

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1.3.5. Mecanismo de acción

La activación de los receptores α-2 produce activación de mecanismos celulares mediados vía proteína G sensible a toxina pertussis (*pertussis toxin-sensitive guanine nucleotide regulatory protein).* Estos mecanismos celulares activados por proteína G parece que varían en función del subtipo de receptor y su localización. El adrenorector α-2A a nivel del *Locus coeruleus* resulta en una retroalimentación negativa disminuyendo actividad de la adenil ciclasa reduciendo así los niveles intracelulares de adenosin monofosfato cíclico (AMPc). Esta reducción de los niveles intracelulares de AMPc y de la protein kinasa dependiente de AMPc provoca defosforilación de canales de calcio. Está alteración en la función de los canales de calcio y la consecuente alteración en el potencial transmembrana condiciona una disminución en la activación neuronal generando sedación. Este mecanismo es parecido al que activan los receptores α-2C, responsables del efecto ansiolítico. Por el contrario, en la vasculatura, el subtipo 2 B produce una estimulación de la actividad de los canales del calcio mediado por el mismo mecanismo efector produciendo vasoconstricción(19).

El mecanismo de acción de dexmedetomidina es único y difiere del resto de fármacos sedantes y analgésicos. Para entender mejor el comportamiento de dexmedetomidina dividiremos los efectos entre aquellos que se originan a nivel de sistema nervioso central, aquellos que se producen a nivel de médula espinal y por último aquellos que afectan a otros órganos en general.

A. Sistema nervioso central

Los receptores α-2 se encuentran repartidos por todo el sistema nervioso central no obstante, la mayor concentración de estos se

encuentran en el *locus coeruleus*, el núcleo noradrenérgico por excelencia del tronco del encéfalo y un importante modulador del estado de vigilia. La activación presináptica del adrenorecptor α-2A en el *locus coeruleus* inhibe la liberación de noradrenalina. La disminución de la liberación de noradrenalina en el *locus coeruleus* permite aumentar la descarga de neuronas inhibitorias sobretodo del sistema gamma aminobutírico responsable de los efectos sedantes e hipnóticos del fármaco. Además, en el *locus coeruleus* se origina una vía descendiente noradrenérgica medulo-espinal, que actúa de forma importante como moduladora de la neurotransmisión nocioceptiva. La estimulación de estos receptores postsinápticos en esta área inhibe la conducción neuronal y disminuye la propagación de los estímulos dolorosos explicando los efectos analgésicos del fármaco. La combinación de estos efectos centrales produce sedación, analgesia y ansiolisis.

Además, la activación postsináptica de los receptores α-2 en el sistema nervioso central disminuye la respuesta simpática originando hipotensión y bradicardia de origen central y aumenta la actividad vagal cardiaca.

B. Médula Espinal.

El efecto analgésico primario y la potenciación del efecto de los opioides que ejerce dexmedetomidina es consecuencia de la activación de receptores α-2 adrenérgicos en el asta dorsal de la médula espinal. La estimulación de los receptores α-2 del asta dorsal inhibe la descarga de neuronas nocioceptivas y inhibe la liberación de sustancia *P*. Además, los receptores α-2 localizados en la terminal nerviosa podrían tener un posible efecto analgésico previniendo la liberación de noradrenalina en la sinapsis. A pesar de que el efecto analgésico primario de la dexmedetomidina depende de los efectos a nivel de

médula espinal, parece que el efecto analgésico global es resultado de la combinación de los dos mecanismos, el espinal y el del sistema nervioso central mediado por el *locus coeruleus*.

C. Otros órganos.

Los receptores α-2 se encuentran también en vasos sanguíneos, en los que provocan vasoconstricción y en terminales simpáticas donde inhiben la liberación de noradrenalina. La activación de adrenoreceptores α-2 en otras localizaciones produce contracción vascular y de otros músculos lisos, disminución de la salivación, disminución de las secreciones, disminución de la motilidad intestinal, inhibición de la secreción de renina, aumento de la filtración glomerular, disminución de la secreción de insulina pancreática, disminución de la presión ocular, disminución de la agregación plaquetar y disminución de unos 2ºC del umbral de temblor.

1.3.6. Farmacocinética de la dexmedetomidina

En adultos, la farmacocinética y farmacodinamia de dexmedetomidina sigue una cinética lineal cuando se infunde a dosis de 0.2 a 0.7 mcg/kg/min. Después de su administración endovenosa en adultos sanos, tiene una fase de distribución (t ½ α) rápida con un tiempo medio de distribución (t ½ β) de 6 minutos; el volumen de equilibrio de distribución es de 1.33 L/kg; un aclaramiento de 0,495 L/kg/h y un tiempo de vida media corto de 2-3 horas. Dexmedetomidina se comercializa para administración endovenosa lo que la hace un fármaco ideal para la utilización en infusión continua. Dexmedetomidina se metaboliza de forma mayoritaria en el hígado vía N-glucoronidación y, en menor medida vía citocromo P-450 (CYP2A6) y N-metilación a metabolitos inactivos (3-hidroxi-dexmedetomidina, 3-

carboxi-dexmedetomidina, 3-hidroxi-N-metil dexmedetomidina, 3-carboxi-N-metil-dexmedetomidina). Según datos de ficha técnica, el aclaramiento de dexmedetomidina en pacientes con disfunción hepática severa fue el 53%, 64% y 74% menor en pacientes con disfunción hepática leve, moderada y severa (Clasificación de Child-Pugh) respectivamente comparada con pacientes sanos, por lo que se recomienda la reducción de dosis en pacientes con disfunción hepática. El 95% de la eliminación de los metabolitos es vía urinaria y el 4% vía fecal. La farmacocinética de dexmedetomidina no se altera de forma significativa en pacientes con disfunción renal severa (aclaramiento de creatinina < 30 ml/min). No existen recomendaciones de dosis en pacientes con disfunción hepática y renal severa por lo que es necesario realizar estudios adicionales en esta población tanto en edad adulta como pediátrica(19-21).

1.3.7. Efectos en órganos terminales. Experiencia clínica.

A. Sistema Nervioso Central.

1. **Sedación, ansiolisis y analgesia**

Numerosos estudios clínicos en humanos y estudios experimentales en animales han demostrado los efectos sedantes de dexmedetomidina. El perfil de sedación conseguido por dexmedetomidina tiene características parecidas a las del patrón normal de sueño. En estudios con resonancia magnética cerebral, la señal dependiente del nivel de oxígeno en sangre, un marcador de la actividad cerebral local, se comporta de la misma manera con la sedación inducida por dexmedetomidina que en el sueño normal, señal muy distinta a la que

aparece con la utilización de otros sedantes como el midazolam. En estudios de experimentación animal utilizando técnicas de inmunohistoquímica y de hibridación in situ, dexmedetomidina induce un patrón de expresión de c-fos en el núcleo cerebral promotor del sueño cualitativamente similar al observado durante la fase del sueño de movimientos oculares no rápidos (disminución en el *locus coeruleus* y un aumento en el núcleo ventrolateral)(22) En un estudio realizado por Nelson y colaboradores, se objetivó la atenuación de estos efectos con la utilización de atipamazol, un antagonista α-2 adrenérgico y, no se llegó a reproducir en animales *knock outs* para el receptor α-2(23). Estos hallazgos son de gran interés puesto que sugieren una vía de sedación similar a la del sueño natural y que se aleja, como se ha comentado anteriormente, de los patrones de sedación producidos por agentes ampliamente utilizados en unidades de cuidados intensivos como benzodiacepinas, barbitúricos, opioides y propofol. Estos últimos producen alteraciones significativas en los patrones electroencefalográficos de sueño y podrían tener una relación con la aparición de delirio.

El efecto analgésico primario y la potenciación del efecto de los opioides es consecuencia de la activación de receptores α-2 adrenérgicos en el hasta dorsal de la médula espinal.

2. **Presión intracraneal y flujo cerebral**

Dexmedetomidina produce un estado de sedación consciente con mínima depresión del centro respiratorio y cierto grado de analgesia que la hace particularmente interesante en todas aquellas situaciones en las que sea importante conseguir una valoración clínica neurológica del paciente. Dexmedetomidina no incrementa la presión intracraneal (PIC)

ni altera la presión de perfusión en pacientes con lesión cerebral. En adultos, dexmedetomidina disminuye el flujo sanguíneo cerebral de forma similar a lo que ocurre en la hiperventilación. Estudios recientes realizados en voluntarios sanos objetivan que la disminución del flujo cerebral se acompaña de una disminución proporcional de la tasa metabólica cerebral lo que sugiere que el balance entre aporte y consumo de oxigeno cerebral, se mantiene estable durante la infusión de dexmedetomidina, convirtiéndole en un fármaco seguro para la administración en situaciones de riesgo neurológico(24).

En animales, la administración vía epidural de dexmedetomidina se ha asociado con la aparición de neurotoxicidad en sustancia blanca. Esta neurotoxicidad se extrapola a la administración vía intranasal. A pesar de que estos resultados no han sido corroborados por otros estudios, sería necesario ser precavidos a la hora de administrar el fármaco vía intranasal.

3. **Umbral de convulsión.**

Los estudios realizados en experimentación animal acerca del umbral de convulsión con dexmedetomidina presentan resultados contrapuestos y no hay un grado de evidencia suficiente para determinar el papel real de dexmedetomidina en relación a las convulsiones.

4. **Neuroprotección**

Hay datos de experimentación animal que sugieren que la utilización de agonistas α-2 adrenérgicos puede mejorar el pronóstico neurológico después de la lesión cerebral isquémica cuando se administra antes o inmediatamente después del inicio de la lesión. Se

trata de un efecto dosis dependiente que resulta reversible con la administración de antagonistas α-2 adrenérgicos y que se correlaciona con la disminución de los niveles de noradrenalina circulante (7,25). Durante la isquemia cerebral, hay una liberación de grandes cantidades de noradrenalina en el líquido extracelular del hipocampo que podría jugar un papel importante en la perpetuación de la lesión cerebral al favorecer la excitabilidad neuronal y el consumo energético cerebral. Además, la noradrenalina facilita y favorece la respuesta de otros mediadores cerebrales excitadores que actúan a través del receptor α-2 adrenérgico e incrementa la respuesta a glutamato que tiene un papel relevante en la lesión neurológica inducida por isquemia. Así pues, la combinación de fármacos que estimulen a los receptores α-2 adrenérgicos y que disminuyan la liberación de noradrenalina y glutamato puede tener un papel relevante en el manejo de la isquemia cerebral (17).

B. Sistema Cardiovascular.

1. Frecuencia cardiaca, presión arterial, gasto cardíaco y contractilidad.

Está descrita la presencia de hipotensión y bradicardia con la administración de dexmedetomidina. Este efecto es más marcado en presencia de disfunción cardiaca de base y en la administración conjunta con otros fármacos con efectos cronotrópicos negativos. En voluntarios sanos la administración de dexmedetomidina se asocia con un efecto bifásico con una fase inicial en la que se objetiva un aumento de la presión arterial y una disminución refleja de la frecuencia cardiaca y seguidamente la frecuencia cardiaca y la tensión arterial se estabilizan en valores inferiores a los basales (19). La hipertensión inicial es

consecuencia de la vasoconstricción secundaria a la estimulación de los receptores periféricos postsinápticos α-2A adrenérgicos. La estimulación de los receptores centrales presinápticos α-2A es la responsable de la disminución de la presión arterial y de la frecuencia cardiaca posterior.

La administración de dexmedetomidina se ha asociado también a la disminución del gasto cardiaco en voluntarios sanos probablemente relacionado con la disminución de la tensión arterial e imposibilidad de aumentar la frecuencia cardiaca de forma refleja. En voluntarios sanos, el gasto cardiaco medido por bioimpedancia torácica fue del 81 ± 13% respecto al basal al minuto y de 91 ± 11% a los 60 minutos de la infusión de una dosis de 1 mcg/kg. Con una dosis de 2 mcg/kg el gasto cardiaco fue de 58 ± 32% al minuto y de 85 ± 28% a los 60 minutos.

El efecto cronotrópico negativo de dexmedetomidina parece potenciarse con la administración concomitante de otros fármacos que disponen del mismo efecto cronotrópico negativo (propofol, succinilcolina, digoxina …) o durante la realización de procedimientos vagotónicos (laringoscopia o fibrobroncoscopia)

Cuando se ha estudiado de forma aislada en experimentación animal, la administración de dexmedetomidina no asocia un efecto inotrópico negativo (28). Por otro lado, la disminución de la frecuencia cardiaca y el consecuente descenso del consumo miocárdico de oxígeno puede resultar beneficioso en pacientes con enfermedad coronaria.

C. Sistema Respiratorio.

Los efectos ventilatorios de dexmedetomidina se han estudiado en voluntarios adultos sanos. La administración de dosis elevadas de dexmedetomidina (1a 2mcg/kg) la $PaCO_2$ incrementa significativamente

con un efecto máximo a los 10 min y una duración de efecto de casi 2 horas. Esto se debe a una disminución del volumen corriente y de la frecuencia respiratoria. La disminución del volumen corriente parece que es de causa obstructiva similar a lo que pasa en el patrón de sueño normal. Al igual que pasa en el sueño normal, con la administración de dexmedetomidna el paciente presenta incrementos periódicos del volumen minuto como respuesta a las oscilaciones de $paCO_2$ (despertar hipercápnico).

Además, disminuye la respuesta broncoconstrictora a agentes irritantes.

D. Sistema nervioso simpático

La administración de dexmedetomidina se asocia a un bloqueo de la respuesta simpática. En pacientes adultos la administración de dexmedetomidina se asocia a una disminución significativa de los niveles de noradrenalina y adrenalina plasmática y urinaria. Este bloqueo de la respuesta simpática puede resultar negativo en situaciones de hipovolemia o hemorragia aguda circunstancias en las que la respuesta simpática es esencial para mantener un adecuado gasto cardiaco.

E. Sistema Gastrointestinal.

Dexmedetomidina enlentece el vaciamiento gástrico según datos obtenidos en experimentación animal.

F. Función Adrenocortical.

Al igual que etomidato, que contiene un anillo imidazol, dexmedetomidina puede inhibir la enzima hidroxilasa esencial en la producción de adrenocorticoides. En modelos animales a las dosis clínicamente avaladas no hay evidencia que sugiera ningún efecto en la

síntesis de esteroides adrenales. Sin embargo, hay estudios que demuestran que a altas dosis dexmedetomidina es capaz de inhibir la producción de esteroides adrenales. En un estudio en adultos en en el que se compara la sedación con propofol vs dexmedetomidina no se observa diferencia en los niveles de cortisol, ACTH, prolactina y glucosa entre los dos grupos. Sin embargo, algunos de los pacientes del grupo dexmedetomidina presentaron curvas de estímulo ACTH anormales. Estas respuestas fueron atribuidas a la enfermedad quirúrgica aguda y no a la dexmedetomidina.

G. Efectos sobre la termorregulación

Dexmedetomidina interfiere en el proceso normal de termorregulación aumentando el umbral del temblor, disminuyendo la vasocontricción y reduciendo la termogénesis. En un estudio realizado en pacientes pediátricos, la administración de dexmedetomidina finalizó los temblores inducidos por la anestesia general en todos los pacientes. La activación de receptores hipotalámicos $\alpha 2$ reduce la producción central de calor. Además, la estimulación de receptores $\alpha 2$ postsinapticos inhibe la lipolisis dificultando así la termogénesis y facilitando la hipotermia. Este impacto sobre la termogénesis hace de dexmedetomidina un fármaco con potencial en el manejo de la hipotermia terapéutica pero la administración en recién nacidos y lactantes debe acompañarse de una estricta monitorización de la temperatura central.

1.3.8. Dexmedetomidina en pediatría

En la actualidad el uso de dexmedetomidina en la población pediátrica no ha sido aprobado en ningún país. Sin embargo, al igual que otros muchos fármacos (dopamina, entre otros) el uso *off-label* de dexmedetomidina como adyuvante a la anestesia perioperatoria o como sedante en las unidades de cuidados intensivos pediátricos se ha extendido ampliamente en la última década. Existen en la literatura científica más de 250 estudios publicados acerca de la utilización de dexmedetomidina en pediatría. A pesar de esta amplia experiencia clínica, debido a la imposibilidad de ampliar de forma eficaz sus indicaciones en pediatría no disponemos de un análisis exhaustivo de su farmacocinética y de sus aplicaiones clínicas.

1.3.9. Aplicaciones clínicas en Pediatría

1. **Sedación en UCI**

La utilización de dexmedetomidina en el control de la sedación en unidades de cuidados intensivos pediátricos permite disminuir la necesidad de opioides(25,26). Existen varios estudios en los que se ha descrito la eficacia de dexmedetomidina como sedante en las unidades de cuidados intensivos pediátricos.

1.a. Sedación para pruebas diagnósticas

La experiencia más amplia en utilización de dexmedetomidina en pediatría es en la sedación para resonancia magnética. En el 90 % de los casos es necesaria la administración de forma coadyuvante de benzodiacepinas.

La utilización de dexmedetomidina durante la realización de estudios electroencefalográficos parece ser de elección. El electroencefalograma durante la infusión de dexmedetomidina es similar al que se objetiva en el estadio 2 de la fase de sueño no REM.

1.b. Sedación para procedimientos

La combinación ketamina con dexmedetomidina ha sido utilizada para la realización de procedimientos en la unidad de cuidados intensivos y parece que puede convertirse en la combinación de elección para procedimientos invasivos en los que se busque mantener el esfuerzo respiratorio y una hemodinamia estable.

2. Control de la abstinencia

En adultos, dexmedetomidina ha sido utilizada ampliamente para el control de la abstinencia. No existen en la literatura pediátrica suficientes datos que respaldan su utilización para este efecto a pesar de que clonidina es uno de los fármacos ampliamente utilizados para este fin. Todavía no disponemos de datos sufientes acerca de los efectos derivados de infusiones largas (más de 5 días) de dexmedetomidina así que parece razonable no hacer una recomendación firme sobre la utilidad de este fármaco en el control de la abstinencia originada por opioides y benzodiacepinas (27–29). Dexmedetomidina ha demostrado su utilidad en el control de la abstinencia por opiáceos en pacientes pediátricos en el postoperatorio de trasplante cardíaco. En una publicación de nuestro equipo de investigación, Laia Vega-Puyal, recogió nuestra experiencia en la utilización de dexmedetomidina en el control de la abstinencia en el paciente trasplantado cardíaco (ANEXO 2-ARTÍCULO 4) recientemente aceptada para publicación.

3. Manejo de la vía aérea difícil

La capacidad de dexmedetomidina de mantener el esfuerzo respiratorio la hace un fármaco atractivo para la intubación en pacientes pediátricos con vía aérea difícil, la realización de laringoscopias y fibrobroncoscopias.

4. Otras indicaciones preoperatorias

Dexmedetomidina se ha utilizado como premedicación previa a la inducción anestésica. La administración oral de dexmedetomidina se ha utilizado de forma efectiva en varios estudios y ofrece resultados similares a los de benzodiacepinas. A pesar de que la vía intranasal ha sido ampliamente utilizada, la aparición de estudios de experimental animal que objetivan neurotoxicidad asociada a la administración epidural hacen extremar la cautela a la hora de recomendar esta vía de administración.

5. Indicaciones Operatorias

5.1. Cirugía Cardiaca

Dexmedetomidina ha sido ampliamente utilizada en cirugía cardiaca de adultos. En niños existen más de 50 estudios acerca de la utilidad de dexmedetomidina en el manejo anestésico perioperatorio de cirugía cardiaca pediátrica. La utilización de dexmedetomidina durante la intervención de cirugía cardiaca pediátrica, al igual que pasa en adultos, disminuye la respuesta hemodinámica y neuroendocrina a la intervención. El bloqueo que produce dexmedetomidina a la respuesta fisiológica al stress puede ser de gran utilidad en cirugía cardiaca.

Dexmedetomidina ha sido utilizada para inducir hipotensión de forma controlada en el postoperatorio de cirugía cardiaca de adultos para disminuir la incidencia de sangrado postoperatorio. Existen en la actualidad publicaciones aisladas en las que se postula el posible beneficio de dexmedetomidina en este sentido.(30–32)

5.2. Neurocirugía

Dexmedetomidina ha sido utilizada en cirugía de craniotomías con el paciente despierto. Permitiendo la ventilación espontánea y la valoración de forma fiable de la respuesta a órdenes. En niños se ha utilizado en cirugía de la epilepsia puesto que mantiene intacta la actividad epileptiforme y lo convierte en un agente adecuado para detectar los focos epileptiformes mediante técnicas de mapeo cortical (33,34).

5.3. Anestesia Regional

A pesar de que existe suficiente literatura que respalda el uso de clonidina en anestesia regional las alarmas suscitadas con la posible toxixidad de dexmedetomidina por vía epidural hacen que hasta que no haya más investigación al respecto no podamos recomendar la utilización de dexmedetomidina como una alternativa segura en anestesia regional.

6. Postoperatorias

La utilización de dexmedetomidina en el control de la sedación en unidades de cuidados intensivos pediátricos permite disminuir la necesidad de opioides(25,26). En un estudio previo realizado por nuestro equipo la utilización de dexmedetomidina en pacientes

pediátricos de más de un año de edad en el postoperatorio de cirugía cardiaca se objetivó bradicardia y/o hipotensión en el 15% de los pacientes. Todos estos episodios fueron tratados de forma efectiva reduciendo o parando la infusión de dexmedetomidina. En un estudio retrospectivo con la utilización de infusiones de dexmedetomidna de larga duración (hasta 15 días), no se objetivaron problemas relacionados con la presión arterial o la frecuencia cardiaca. Estos datos sugieren que dexmedetomidna es un fármaco seguro de administrar incluso en pacientes pediátricos de > 1 año de edad en situación de riesgo cardiovascular siempre que las dosis se ajusten al estado cardiovascular del paciente. En este sentido, la literatura es todavía escasa en la población de lactantes y neonatos en situaciones especiales que puedan asociar compromiso circulatorio como puede ser el postoperatorio de cirugía cardiaca. En este sentido el primer estudio publicado aporta datos acerca de la utilización de dexmedetomidina en esta población de neonatos o lactantes de riesgo.

2. HIPÓTESIS Y OBJETIVOS

El objetivo de esta tesis es el de recoger toda la experiencia en la utilización de dexmedetomidina en el postoperatorio de cirugía cardíaca pediátrica por nuestro equipo investigador y presentar los hallazgos clínicos que constatan su papel antiarritmogénico.

Hipótesis:

La utilización de dexmedetomidina en pacientes pediátricos en el postoperatorio de cirugía cardíaca es útil para el manejo y la prevención de la taquiarritmia.

Objetivos concretos:

1.- Demostrar eficacia y seguridad de dexmedetomidina en población de pacientes pediátricos de menor edad (<2 años) en el postoperatorio de cirugía cardiaca. (ARTÍCULO 1)

2.- Demostrar la utilidad de la dexmedetomidina en el tratamiento de la taquiarritmia. (ARTÍCULO 2)

3.- Demostrar la utilidad de la demedetomidna en la prevención de la taquiarritmia en el postoperatorio de cirugía cardiaca. (ANEXO 1-ARTÍCULO 3)

3. ARTÍCULOS

En este contexto la *Comissió d'Estudis de Postgrau de la Universitat Autònoma de Barcelona*, en la resolución efectuada el 18 de julio de 2012 aceptó la presentación de la Tesis: *Utilitat dels agonistes α-2 en la prevenció de la taquiarritmia en el postoperatori de cirurgía cardiaca pediátrica,* en formato de Compendio de publicaciones con las tres siguientes publicaciones:

1) ***Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery****? Pediatr Crit Care Med*. 2009 Nov; 10 (6): 654-60. Erratum in: Pediatr Crit Care Med. 2012 May;13(3):373.Vol. 10, No. 5

2) ***Dexmedetomidine: Therapeutic Use for the Termination of Reentrant Supraventricular Tachycardia.*** *Congenit Heart Dis*. 2012 May 22. doi: 10.1111/j.1747-0803.2012.00669.x. [Epub ahead of print]

3) **Perioperative Use of Dexmedetomidine Is Associated With Decreased Incidence of Ventricular and Supraventricular Tachyarrhythmias After Congenital Cardiac Operations.** *Ann Thorac Surg*. 2011; Sep;92(3):964 –72

3.1. ARTÍCULO 1

1) ***Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery****? Pediatr Crit Care Med.* 2009 Nov; 10 (6): 654-60. Erratum in: Pediatr Crit Care Med. 2012 May;13(3):373.Vol. 10, No. 5

ERRATA

Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery?: Erratum

In the article on page 654 of the November 2009 issue, Dr. Sanchez De Toledo's full affiliation should have been listed as follows:

From the Department of Pediatrics and Critical Care Medicine, Division of Cardiac Intensive Care, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, PA; and Pediatric Cardiac Intensive Care, Hospital vall d'Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain.

REFERENCE

Chrysostomou C, Sanchez De Toledo J, Avolio T, et al: Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery? *Pediatr Crit Care Med* 2009; 10:654–660

In the March 2012 issue, one of the authors was incorrect for three separate articles. In the following articles, it should have been M. Jayashree.

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Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery?

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Objective: To assess clinical response of dexmedetomidine alone or in combination with conventional sedatives/analgesics after cardiac surgery.

Design: Retrospective study.

Setting: Pediatric cardiac intensive care unit.

Patients: Infants and neonates after cardiac surgery.

Measurements and Main Results: We identified 80 patients including 14 neonates, at mean age and weight of 4.1 ± 3.1 months and 5.5 ± 2 kg, respectively, who received dexmedetomidine for 25 ± 13 hours at an average dose of 0.66 ± 0.26 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Overall normal sleep to moderate sedation was documented 94% of the time and no pain to mild pain 90%. Systolic blood pressure (SBP) decreased from 89 ± 15 to 85 ± 11 mm Hg ($p = 0.05$), heart rate (HR) from 149 ± 22 to 129 ± 16 bpm ($p < 0.001$), and respiratory rate (RR) remained unchanged. When baseline arterial blood gases were compared with the most abnormal values, pH decreased from 7.4 ± 0.07 to 7.37 ± 0.05 ($p = 0.006$), Po_2 from 91 ± 67 to 66 ± 29 ($p = 0.005$), and CO_2 increased from 45 ± 8 to 50 ± 12 ($p = 0.001$). At the beginning of the study, 37 patients (46%) were mechanically ventilated, and at 48 hours 13 patients (16%) were still intubated and five patients failed extubation. Three groups of patients were identified: A, dexmedetomidine only (n = 20); B, dexmedetomidine with sedatives/analgesics (n = 38); and C, dexmedetomidine with both sedatives/analgesics and fentanyl infusion (n = 22). The doses of dexmedetomidine and rescue sedatives/analgesics were not significantly different among the three groups but duration of dexmedetomidine was longer in group C vs. A ($p = 0.03$) and C vs. B ($p = 0.002$). Pain, sedation, SBP, RR, and arterial blood gases were similar. HR was higher in group C vs. B ($p = 0.01$). Comparison between neonates and infants showed that infants required higher dexmedetomidine, 0.69 ± 25 vs. 0.47 ± 21 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($p = 0.003$) and had lower HR ($p = 0.01$), RR ($p = 0.009$), and higher SBP ($p < 0.0010$).

Conclusions: Dexmedetomidine use in infants and neonates after cardiac surgery was well tolerated in both intubated and nonintubated patients. It provides an adequate level of sedation/analgesia either alone or in combination with low-dose conventional agents. (Pediatr Crit Care Med 2009; 10:???–???)

KEY WORDS: sedation; analgesia; infants; dexmedetomidine; cardiac surgery; intensive care unit

Providing sedation and analgesia in children after cardiac surgery can be challenging. Although our knowledge about sedative agents and their cardiorespiratory interactions has improved during the last two decades, delivering optimal sedation in the postoperative period remains complex. Some of the factors that add to this complexity are the presence of an unpredictable and potentially labile physiology after cardiopulmonary bypass and the inability to accurately assess an infant's level of sedation.

In our institution, a successful effort for fast track and early extubation has been in place for the last 5 years. Nonetheless, a significant proportion of patients remain, who could further benefit from newer sedative agents with a better safety profile and less respiratory depression. This is important for infants with both univentricular and biventricular physiology and particularly the ones which are extubated or near extubation. Dexmedetomidine is a highly specific alpha-2 adrenergic receptor agonist with sedative, analgesic, and anxiolytic properties (1). It does not appear to significantly depress respiratory drive, thus interference with weaning from mechanical ventilation is less likely. In fact, it has been used both as a bridge to extubation as well as in nonintubated patients (2, 3). In our previous study, which was mainly focused on older children after cardiothoracic surgery, dexmedetomidine was found to be well tolerated and provided targeted sedation and analgesia in 93% and 83% of the time, respectively (2). In this article, we describe our experience with the use of dexmedetomidine in a much younger and rather more difficult population, infants, and neonates after congenital cardiac surgery.

MATERIALS AND METHODS

This retrospective, case series study was approved by the Institutional Review Board of the University of Pittsburgh Medical Center/Children's Hospital of Pittsburgh. To follow our institution's policy, parental informed consent for investigational use of a drug was obtained for all patients younger than 1 year. Infants and neonates who were admitted to the cardiac intensive care unit (CICU) from

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This study was performed at Cardiac Intensive Care Unit, Children's Hospital of Pittsburgh/University of Pittsburgh Medical Center.

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January 2004 to May 2007 and had received dexmedetomidine were included.

Dexmedetomidine was started as a continuous infusion, at a dose of 0.1–1.25 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. If it was considered necessary, a 1 $\mu g/kg$ bolus at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was given. According to the clinical practice in our CICU, the decision whether to give a bolus and the exact initial infusion dose was based on the physician's judgment and the level of sedation that the patient had before the initiation of the infusion, i.e., the degree of residual intraoperative anesthesia. Twenty minutes after the onset of the infusion, if sedation/analgesia were considered inadequate, by the bedside nurse and by the physician on duty, dexmedetomidine infusion was increased by 0.1–0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. If sedation/analgesia were still inadequate 20 minutes after the change of the infusion dose, a rescue agent was administered if necessary, and dexmedetomidine infusion was further increased to a maximum of 1.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The maximum infusion dose of 1.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, was a consensus decision among the intensivists and pharmacists involved with the care of CICU patients. Given the lack of an established sedation protocol and the diversity of our patient population, the rescue agents were multiple and included fentanyl, morphine, midazolam, lorazepam, ketamine, and chloral hydrate.

Heart rate (HR), systolic blood pressure (SBP), respiratory rate (RR), and sedation and analgesia scores were recorded by the nursing staff at baseline, i.e., measurement within 1 hour before starting dexmedetomidine, and every hour thereafter. Arterial blood gas (ABG) results were also recorded every 1–4 hours as clinically indicated. A hypertensive or hypotensive episode was defined as a 30% change from baseline and/or if the SBP was below or above the 5th to 95th percentile for age. A bradycardic episode was defined as a 30% change from baseline and/or if the HR was below the fifth percentile for age. Low RR rate was defined as a RR below the fifth percentile for age. Sedation was assessed using a pediatric intensive care unit sedation scale ranging from 0 to 3 (0, none, alert, or normal sleep, easy to arouse; 1, mild sedation, occasionally drowsy, easy to arouse; 2, moderate sedation, frequently drowsy but easy to arouse; 3, severe sedation, somnolent, difficult to arouse). Analgesia was assessed with two 0–10 pain score scales: the FLACC (face, legs, activity, cry, and consolability) for patients older than 2 months old, and the CRIES (cries, requires oxygen for saturation less than 95%, increased vital signs, expression, sleepless) for patients 0–6 months old (4, 5). A pain score of 0 was considered pain free, 1–3 mild pain, 4–7 moderate pain, and 8–10 severe pain. The targeted level of sedation and analgesia was 0–2 and 0–3, respectively. Data were collected for as long as the dexmedetomidine infusion was being administered to a maximum of 48 hours.

Absolute exclusion criteria for the use of dexmedetomidine included decompensated heart failure, acute hemodynamic instability, septic shock, and ventricular arrhythmias. Relative exclusion criteria included a high RACHS-1 (risk adjustment for congenital heart surgery) score, 5 and 6 (6).

Patients were divided into three groups: A, dexmedetomidine only (n = 20); B, dexmedetomidine with sedatives/analgesics (n = 38); and C dexmedetomidine with both sedatives/analgesics and fentanyl infusion (n = 22). Three major comparisons of data were performed: between baseline and while on dexmedetomidine infusion; among groups A, B and C; and between neonates and infants. Baseline vital signs were compared with the lowest values and baseline ABGs with the lowest pH, base excess, Po_2 and the highest CO_2 levels while receiving dexmedetomidine. Categorical variables were reported as frequencies and percentages. Continuous variables were reported as mean ± sd if the distribution was normal and as median with range if the distribution was not normal. Paired Student's *t* test or the Wilcoxon test, depending on the distribution of the data being analyzed, was used to compare continuous variables before and during dexmedetomidine infusion. Groups A, B, and C, were analyzed by the analysis of variance test or Kruskal-Wallis test, depending on the distribution, followed by the Bonferroni equation or the Dwass-Steel-Critchlow-Fligner test, respectively, for in between group differences. Pain and sedation scores were analyzed by analysis of variance based on Kruskal-Wallis. Data from neonates and infants were either analyzed by an unpaired Student's *t* test or the Mann-Whitney test. Pearson's correlation coefficient (*r*) was used to identify any correlation between dexmedetomidine dose and vital signs. All reported *p* values were two-tailed, and values of $\alpha \leq 0.05$ were considered statistically significant.

Table 1. Cardiac diagnosis/procedures performed

	n (%)
Tetralogy of fallot	19 (24)
Coarctation of the aorta	14 (17.5)
VSD with or without ASD	12 (15)
Atrioventricular septal defect	9 (11)
Glenn	9 (11)
Hypoplastic or interrupted aortic arch and VSD	3 (4)
Norwood stage I (HLHS)	2 (2.5)
Total anomalous pulmonary venous return	2 (2.5)
Pulmonary valvotomy and VSD	2 (2.5)
Blalock-Taussig shunt	2 (2.5)
Transposition of the great arteries	1
Aortopulmonary window	1
Right ventricle to pulmonary artery conduit	1
Left pulmonary artery augmentation	1
Other*	2

ASD, atrial septal defect; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect.
*One patient s/p cardiac catheterization and one with severe pulmonary hypertension.

RESULTS

A total of 80 patients (39 males and 41 females) were identified (Tables 1 and 2) and divided into three groups: A, n = 20; B, n = 38; C, and n = 22. Four of these patients were included in our previous report (2). Overall there were 1999 individual hourly points of data collected.

Average age and weight were 4.1 ± 3.1 months and 5.5 ± 2 kg, respectively. Group B had a higher weight compared with group C ($p = 0.01$). Fourteen patients (17.5%) were neonates with a mean age and weight of 15 ± 9 days and 3.2 ± 0.9 kg, respectively. Seventy-eight surgical procedures were adjusted for se-

Table 2. Baseline patient characteristics

	Group A (n = 20)	Group B (n = 38)	Group C (n = 22)	*p*
Age (mo)	3.9 ± 3	4.8 ± 3	3.2 ± 3	0.12
Weight (kg)	5.5 ± 2	6.1 ± 1.9	4.4 ± 2	0.01[a]
Gender (M, F)	9, 11	18, 20	15, 7	
Mechanically ventilated, n (%)				
On admission	8 (40)	11 (29)	18 (82)	
At 48 hrs	3 (15)	3 (8)	7 (32)	
Vital signs				
HR (bpm)	149 ± 19	146 ± 23	152 ± 24	0.52
SBP (mm Hg)	85 ± 12	88 ± 15	82 ± 18	0.03[b]
RR (breaths/min)	32 ± 13	32 ± 12	29 ± 12	0.7
CICU length of stay (d)	4 (1–126)	3 (1–87)	8 (2–74)	0.005[c]

CICU, cardiac intensive care unit; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure.
[a]$p = 0.002$ group B vs. C; [b]$p = 0.046$ group A vs. B and $p = 0.017$ group B vs. C; [c]$p = 0.002$ group B vs. C.

verity according to RACHS-1 classification and the median severity score was 2 (range, 1–6). The total CICU length of stay was a median of 4 days (1–126). Group B had a shorter CICU stay when compared with group C ($p = 0.002$) (Table 2).

Dexmedetomidine Dosing and Duration. Dexmedetomidine was started at a mean of 4 ± 6 hours after arrival from the operating room. A total of 24 patients (30%) received a 0.5–1 μg/kg loading dose at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The mean dexmedetomidine starting dose was 0.47 ± 0.29 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ followed by a maintenance infusion of 0.66 ± 0.26 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The duration of infusion was 25 ± 13 hours.

Dexmedetomidine dose requirement between mechanically ventilated and nonmechanically ventilated patients did not differ, 0.62 ± 0.26 vs. 0.68 ± 0.26 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($p = 0.3$). Similarly, there was no difference in dexmedetomidine dose between patients who received fentanyl infusion (group C) and those who did not (groups A and B), 0.6 ± 0.21 vs. 0.68 ± 0.28 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($p = 0.2$) (Table 3). Dexmedetomidine duration, however, was longer in group C compared with A ($p = 0.03$) and compared with B ($p = 0.002$).

To assess if cumulative experience with the use of dexmedetomidine could have resulted in higher doses, we compared the dexmedetomidine dosage between the first and the last 40 patients. Both starting and maintenance doses were significantly higher in the last 40 patients. Starting dose was 0.34 ± 0.18 vs. 0.6 ± 0.32 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($p < 0.001$) and maintenance dose was 0.54 ± 0.2 vs. 0.78 ± 0.26 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ ($p < 0.001$). Furthermore, we analyzed the amount of times dexmedetomidine was administered above the recommended adult maximum dose of 0.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. There were a total of 789 recorded doses (39% of dexmedetomidine infusion time) above the maximum, the majority of which (>75%) were in the last 40 patients, 169 vs. 620.

Rescue Sedative/Analgesic Agents. Groups A and B, which comprised 73% of patients, received dexmedetomidine without any other continuous analgesic or sedative infusion. Group C, had an average fentanyl infusion dose of 1.7 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ and it continued for 18 ± 15 hours. Table 3 shows in detail the requirements of these three groups. There was no significant difference in rescue sedation/analgesia, between patients who received fentanyl infusion and patients who did not, 2.8 vs. 2.6 doses per 24 hours of dexmedetomidine infusion, respectively. Overall, fentanyl (40%), morphine (20%), and chloral hydrate (15%) were the most common rescue drugs used. Midazolam, lorazepam, and ketamine were used less frequently.

Table 3. Descriptive data on sedatives, analgesics, and hemodynamic infusions among groups A, B, and C during dexmedetomidine infusion

	Group A (n = 20)	Group B (n = 38)	Group C (n = 22)	p
Dexmedetomidine				
Dose (mcg/kg/hr)	0.72 ± 0.31	0.65 ± 0.26	0.6 ± 0.21	0.37
Duration/patient (hrs)	24 ± 12	22 ± 11	32 ± 15	0.009[a]
Duration (total patient hrs)	471	820	708	
Fentanyl (mcg/kg/hr)			1.7 ± 1	
Rescue doses[b] (doses/24 DEX infusion hrs)		143 (2.6)	84 (2.8)	
Analgesics (n)		106	46	
Sedatives (n)		37	38	
Milrinone, n (%)	16 (80)	30 (79)	20 (91)	
Dose (mcg/kg/min)	0.91 ± 0.24	0.86 ± 0.24	0.84 ± 0.26	0.68
Duration (hrs)	23 ± 11	24 ± 11	32 ± 15	0.06
Dopamine, n (%)	2 (10)	8 (21)	6 (27)	
Dose (mcg/kg/min)	2.9 ± 3.1	3.3 ± 0.8	3.7 ± 1.2	0.9
Duration (hrs)	5 ± 6	13 ± 9	16 ± 8	0.27
Epinephrine, n (%)	0	1 (2)	2 (9)	
Dose (mcg/kg/min)		0.04	0.03 ± 0.02	
Duration (hrs)		14	26 ± 20	
Nitroprusside, n (%)	10 (50)	30 (71)	7 (32)	
Dose (mcg/kg/min)	2.2 ± 1	2.2 ± 1	1.6 ± 0.7	0.37
Duration (hrs)	18 ± 10	12 ± 7	16 ± 7	0.16
Esmolol, n (%)	0	3 (7)	0	
Dose (mcg/kg/min)		157 ± 42		
Duration (hrs)		14 ± 7		

DEX, dexmedetomidine.

[a]$p = 0.03$ group A vs. C and $p = 0.002$ group B vs. C; [b]group A and Group B rescue doses are presented as one group; Values are presented as mean ± SD.

Table 4. Sedation and pain scores

	Group A (n = 20)	Group B (n = 38)	Group C (n = 22)	p
Sedation score (0–3)	1.0 ± 0.4	1.2 ± 0.5	1.4 ± 0.4	0.28
Pain score (0–10)	1.7 ± 0.9	2.0 ± 1	1.9 ± 0.7	0.62

Values are presented as mean ± SD.

Sedation/Analgesia. The overall mean sedation score was 1.2 ± 0.5. Normal sleep, defined as easily arousable patient without drowsiness, to moderate sedation was documented 94% of the time. In regards to analgesia, the mean pain score was 1.9 ± 0.9 and no pain to mild pain was documented 90% of the time. Among groups A, B, and C, sedation and pain scores were similar (Table 4).

Cardiorascular Effects. Average SBP and HR were statistically lower after dexmedetomidine was initiated. Blood pressure decreased from 89 ± 15 at baseline, to an average of 85 ± 11 mm Hg (5% decrease, $p = 0.006$). HR decreased from 149 ± 22 to 129 ± 16 bpm (13% decrease, $p < 0.001$) (Fig. 1). Further analysis between baseline and average lowest values showed a decline in the SBP to 69 ± 11 mm Hg (22% decrease) and HR to 113 ± 15 bpm (24% decrease). Changes in dexmedetomidine dose, correlated negatively with HR ($r = -0.65$, $p < 0.001$), and had no correlation with SBP ($r = -0.2$, $p = 0.22$).

Because of lack of data and because the timing of starting dexmedetomidine was not uniform in all patients after surgery, it was difficult to differentiate if hemodynamic changes were secondary to a potential presence of low cardiac output syndrome (LCOS) or dexmedetomidine. Nonetheless, the HR trend and the correlation with dexmedetomidine dosage did not support a worsening LCOS because of dexmedetomidine (Fig. 1). As noted above, the overall HR was lower after initiating dexmedetomidine, in contrast

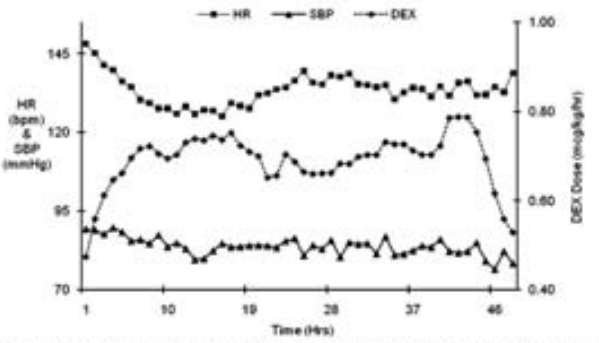

Figure 1. Average heart rate (*HR*), systolic blood pressure (*SBP*), and dexmedetomidine (*DEX*) dose in all patients.

Table 5. Hemodynamic variables in groups A, B, and C during dexmedetomidine infusion

	Group A (n = 20)	Group B (n = 38)	Group C (n = 22)	*p*
SBP (mm Hg)	85 ± 9	88 ± 11	82 ± 11	0.19
HR (bmp)	128 ± 15	126 ± 13	136 ± 17	0.03*
RR (br.pm)	32 ± 8	30 ± 8	34 ± 11	0.34

SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate.
*$p = 0.01$ group B vs. C. Values are presented as mean ± sd.

to the expected higher HR seen in LCOS state (7). Additionally, we noticed that during the first 8 hours, when dexmedetomidine dose increased steadily, there was a large negative correlation with HR ($r = -0.9$, $p < 0.001$). During the 9- to 17-hour period, there was no correlation ($r = 0.04$, $p = 0.9$) and during the 18- to 28-hour period, when there was a steady decline in the dexmedetomidine dose, there was also a significant negative correlation ($r = -0.7$, $p = 0.07$). These indirect findings do not support worsening LCOS. Figure 1 shows graphically the HR and SBP trend in relation to dexmedetomidine dose and duration. Because vital signs were documented only every hour, we were not able to detect further changes that may have occurred during the loading dose or with increased dexmedetomidine infusion rate.

Twenty-seven patients (34%) had at least one episode of hypotension and 10 patients (12.5%) at least one episode of bradycardia. Overall, from the 1999 hourly recordings, there were 58 hypotensive events (3%) and 44 bradycardic events (3%). Crystalloid or colloid fluids boluses were administered in 23 patients (29%); however, we could not determine whether these were a part of the postoperative cardiac care or if they were associated with dexmedetomidine administration.

Sixty-six patients were on some inotropic support before dexmedetomidine was started. Table 3 shows the inotropic agent requirements among groups A, B, and C and Table 5 shows the hemodynamic variables. Overall there was no substantial difference in the hemodynamic infusions, SBP or RR. HR was statistically higher in group C compared with group B ($p = 0.01$). A total of 50 patients had significant postoperative systemic hypertension requiring sodium nitroprusside (47 patients) and esmolol (three patients). Thirty-three of these belonged to group B.

Nine patients had an arrhythmia before starting dexmedetomidine. The types of arrhythmias included five patients with junctional ectopic tachycardia, two with first and one with third-degree atrioventricular block, and one patient with junctional accelerated rhythm. All arrhythmias recovered to normal sinus rhythm before discharge from the CICU.

Respiratory Effects. Thirty-seven patients (46%) were already intubated at the initiation of the dexmedetomidine infusion. Twenty-four of these were weaned off and extubated while receiving dexmedetomidine. Five patients subsequently failed extubation while receiving dexmedetomidine. Three had complex CICU courses, with chronic lung disease and previous prolonged intubation and two were found to have hemidiaphragm paralysis that needed surgical intervention.

Among the patients who were not intubated at the initiation of dexmedetomidine, none required intubation during the study period. None of the patients had any documented episodes of apnea.

There was no significant change between baseline and overall mean RR, 31 ± 12 to 31 ± 9 breaths/min ($p = 0.83$). However, a comparison between baseline and the lowest mean RR, 20 ± 6 (35% drop) showed a significant difference ($p < 0.001$). There were 31 patients with 108 recorded episodes consistent with low RR for age (5% incidence). When we analyze dexmedetomidine dose in relation to the RR, we did not find any significant correlation ($r = -0.05$, $p = 0.76$).

ABGs were statistically different when baseline values were compared with the most abnormal ABGs while on dexmedetomidine. These changes included lower pH level, 7.40 ± 0.1 to 7.37 ± 0.1 ($p = 0.006$), mild CO_2 retention, 45 ± 8 to 50 ± 12 ($p = 0.001$), and lower Po_2 levels, 91 ± 67 to 66 ± 29 ($p = 0.005$). The timing of these most abnormal ABGs ranged from 2 to 25 hours after starting dexmedetomidine, with an average of 4 ± 7 hours. These ABG changes did not differ among groups A, B, and C (Table 6).

Gastrointestinal Effects. Twenty-one patients (26%) were fed during the dexmedetomidine infusion. One episode of vomiting was documented in one patient.

Neonates vs. Infants. A subgroup analysis was performed comparing neonates (n = 14) with infants (n = 66) (Table 7). Dexmedetomidine dose was statistically lower in neonates ($p = 0.003$). Sedation and analgesia scores and rescue sedatives were similar in both groups. HR and RR were statistically higher and SBP was lower in neonates.

Safety and Adverse Events. Two patients had changes in the cardiorespiratory variables that may have been attributed to dexmedetomidine and thus it was discontinued. The first was a 2-month-old patient with aortic coarctation repair who had received dexmedetomidine for 8 hours before discontinuation (0.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). At the time, this patient was simultaneously treated with nitroprusside (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for hypertension when a dose of hydralazine was ad-

Table 6. Comparison of arterial blood gas changes in groups A, B, and C

	Group A (n = 20)	Group B (n = 38)	Group C (n = 22)	*p*
pH				
Baseline	7.4 ± 0.06	7.41 ± 0.06	7.39 ± 0.09	0.6
Lowest	7.37 ± 0.05	7.38 ± 0.05	7.36 ± 0.06	0.2
CO_2				
Baseline	45 ± 6	46 ± 7	45 ± 11	0.9
Highest	54 ± 19	48 ± 8	50 ± 8	0.4
Po_2				
Baseline	86 ± 54	100 ± 72	79 ± 71	0.1
Lowest	73 ± 36	69 ± 26	55 ± 25	0.07
Base excess				
Baseline	2 ± 4	4 ± 4	3 ± 6	0.4
Lowest	1 ± 4	2 ± 4	1 ± 3	0.5

Values are presented as mean ± SD.

Table 7. Neonates vs. infants

	Neonates (n = 14)	Infants (n = 66)	*p*
Group A, B, C (n)	3, 7, 4	17, 15, 34	
Dexmedetomidine			
Dose (mcg/kg/hr)[a]	0.47 ± 21	0.69 ± 25	0.003
Duration (hrs)[a]	27 ± 17	25 ± 13	0.6
Rescue sedative/analgesic doses n (doses/24 DEX infusion hrs)	43 (2.6)	184 (2.7)	
Pain score[b]	2 (0.5–2.4)	2 (0–4)	0.5
Sedation score[b]	1.4 (0–2)	1 (0–2.3)	0.06
Vital signs			
HR (bpm)[a]	140 ± 10	127 ± 15	0.001
SBP (mm Hg)[a]	77 ± 9	87 ± 10	< 0.001
RR (br.pm)[b]	37 (17–55)	28 (18–68)	0.009
RACHS–1[b]	3 (1–4)	2 (1–6)	0.1
CICU stay (d)[b]	8 (2–30)	4 (1–126)	0.67

DEX, dexmedetomidine; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; CICU, cardiac ICU; RACHS-1, Risk Adjustment for Congenital Heart Surgery Classification.

[a]Values as mean ± SD; [b]values as median with range.

ministered. The patient's SBP decreased from a baseline of 81 to 65 mm Hg, a 19% change and the decision was made to discontinue both the nitroprusside and dexmedetomidine infusions. Blood pressure returned to baseline within 15 minutes. The second patient was also a 2-month old with coarctation of the aorta repair who had received dexmedetomidine for 11 hours (0.7 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$). The patient's HR had decreased from baseline of 115 to 89 bpm, a 23% change and although normotensive at the time with no signs of LCOS, a precautionary decision was made by the physician on call to discontinue dexmedetomidine. HR recovered to 127 bpm within 1 hour without any further interventions.

DISCUSSION

Dexmedetomidine has been increasingly used in our CICU for sedation, analgesia, and other off-label indications. With growing experience, we have expanded its use from adolescents and young adults to infants and neonates, and to more complex cardiac surgeries. In our previous study, although only seven patients were younger than 1 year, we noticed that this younger population had a tendency toward a higher dexmedetomidine dose requirement (2).

In this report, which included only infants and neonates, dexmedetomidine dose was higher compared with our previous results in older children, 0.66 vs. 0.4 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$ (2). We also found that with increasing experience, the dose had increased to 0.78 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$. Although these dose ranges are relatively high, they are still within the range published in both adult and pediatric literature (8–10). Two pediatric pharmacokinetic studies by Petroz et al (11) and Díaz et al (12), although limited by the number of infants included, showed that children had similar and predictable pharmacokinetics compared with adults. In reference to our minority neonatal subgroup of patients, we found that dexmedetomidine dose was lower compared with the older infant population. Given the small number of patients, we can only speculate why there was such a difference. One possibility is that due to the immature neonatal kidney function, the renally excreted dexmedetomidine accumulates over time and thus the requirement is less. The lower SBP and higher RR and HR are likely explained by the age difference.

Dexmedetomidine decreases opioid and benzodiazepine requirements, possibly due to a synergistic or additive effect, and in some studies it has been used as a single agent for sedation (13, 14). In 25% of the patients in this report, dexmedetomidine was administered as the sole sedative/analgesic agent; approximately half of the patients required occasional rescue boluses and 27% required an additional low-dose fentanyl infusion. A comparison between patients who received additional fentanyl infusion and those who did not showed that there was no difference in either sedation or pain score and both groups received equal amount of rescue sedative/analgesic boluses. Providing an adequate level of analgesia with the least amount of side effects is of paramount importance, and has been shown to decrease cardiorespiratory morbidity and, therefore, hospitalization time. This is rather important, taking into consideration that most CICU patients have several noxious stimuli including chest tubes and chest incisions as well as the need for mechanical ventilation. Our results are in agreement with Tobias and Berkenbosch (15), who demonstrated that the use of dexmedetomidine in pediatric ICU patients was superior to midazolam infusion based on supplemental rescue dose requirements. The study by Tobias was a small randomized trial, in mechanically ventilated infants and children, and it compared dexmedetomidine infusion at two different doses, 0.25 and 0.5 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$ with midazolam 0.22 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$. At a dose of 0.25 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$, dexmedetomidine was equivalent to midazolam. At 0.5 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$, dexmedetomidine provided more effective sedation as demonstrated by the need for fewer bolus doses of morphine, a decrease in the 24-hour requirements for supplemental morphine, as well as a decrease in the total number of sedation assessment points outside of the desired range.

Dexmedetomidine causes minimal respiratory depression, making it a potentially useful agent in nonintubated patients. Overall, 95% of the patients in this study who were either nonintubated at baseline or extubated while receiving dexmedetomidine had no clinically significant respiratory compromise. Five patients who failed extubation had other significant underlying pathologies and their failure was not directly attributed to dexmedetomidine. Nevertheless, in contrast to our previous study, we did see changes in the respiratory variables, and although transient, they still warrant attention. These changes included mild hypercapnia, lower pH, and P_{O_2} levels and lower RR. These results are consistent with findings from earlier studies by other authors, where it was shown that both low- and high-dexmedetomidine bolus, 0.25 and 2 μg/kg, decreased resting ventilation and ventilatory response to hypercapnia (16). Other studies also demonstrated that dexmedetomidine can cause mild decreases in the P_{O_2} levels or oxygen saturation, and mild hypercapnia (17). In the majority of the times, these respiratory changes are clinically insignificant. However, caution is warranted since such alterations can potentially cause significant fluctuations in the pulmonary vascular resistance and thus change the hemodynamic profile in patients with single ventricle physiology as well as in patients with potentially labile pulmonary vascular resistance, i.e., after repair of complete atrioventricular septal defect, truncus arteriosus, etc.

The more frequently reported adverse events associated with dexmedetomidine include a dose-related hypotension and bradycardia (13, 17, 18). In this study, the prevalence of these side effects was similar to that reported in the literature. In general, there was only a small drop in the SBP and HR, but transiently we saw up to 22% and 24% changes, respectively. A recent small, prospective study by Hammer et al (19) investigated the electrophysiologic effects of dexmedetomidine in 12 children who underwent cardiac catheterization for possible ablation. Although the study was performed in the presence of ketamine and propofol, both of which may have a negative electrophysiologic effect, Hammer et al found that dexmedetomidine depressed both sinus and atrioventricular nodal function. Dexmedetomidine appears to have a wide safety margin; however, its sympatholytic properties should be respected and it should be used with extreme caution in patients at risk for any bradyarrhythmias, and in patients who are receiving medications that cause vasodilation or have negative chronotropic effects (20, 21).

A less frequent adverse effect described in adults is nausea and vomiting. In this study, there was only one episode of vomiting and a quarter of the patients were fed without symptoms. Dexmedetomidine, unlike opioids, does not reduce enteral motility significantly, and thus development of ileus is less likely. This is a significant advantage, especially in the neonatal and infant population, because patients can be well sedated and comfortable and still receive enteral nutrition.

Study Limitations. There are several limitations in this study that should be considered when using dexmedetomidine after pediatric cardiac surgery. The majority of the patients included had mild to moderate surgical risk and thus its use in more complex, potentially unstable physiologies is still not established. There was a lack of objective data regarding ventricular function and cardiac output and although dexmedetomidine does not seem to have a direct negative inotropic effect, some studies have shown that it can decrease cardiac output by means of decreasing HR (18). There was no control group for direct comparison of both hemodynamic data and efficacy of sedation and analgesia. Finally, the neonatal group remains a distinctive patient population, and although our overall results appear to show that dexmedetomidine was well tolerated, the number of neonates in this study was relatively small for any meaningful conclusions.

CONCLUSION

This is one of the largest studies on the use of dexmedetomidine in infants and neonates after cardiac surgery. Based on our experience so far, we have found dexmedetomidine to be well tolerated and effective and that it can be used either alone or in conjunction with other sedatives, in both intubated and nonintubated cardiac patients. Caution, however, is still warranted since large prospective, randomized studies in this young patient population are lacking.

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Objetivo:

Analizar el uso de dexmedetomidina como agente sedante sólo o en combinación con otros agentes sedoanalgésicos en el postoperatorio de cirugía cardíaca pediátrica.

Diseño:

Estudio retrospectivo

Periodo:

Enero 2004 a Mayo 2007.

Población:

Neonatos y pacientes pediátricos menores de 1 año en el postoperatorio de cirugía cardiaca ingresados en la unidad de cuidados intensivos cardiacos. Los pacientes fueron divididos en tres grupos: A, dexmedetomidina sola (n=20); B, dexmedetomidina combinada con sedantes/analgésicos (n=38); y C, dexmedetomidina con sedantes/analgésicos y infusión de fentanilo (n=22). Se hicieron comparaciones de variables hemodinámicas entre: 1) los valores basales y los valores durante la infusión de dexmedetomidina en los tres distintos grupos; 2) entre los grupos A, B y C y 3) entre pacientes neonatales y pediátricos.

Resultados:

Se incluyeron un total de 80 pacientes (14 neonatos) con edad media de 4,1 ± 3,1 meses y pesos medios de 5,5 ± 2 kg que recibieron dexmedetomidina durante 25 ± 13 horas a una dosis media de 0,66 ± 0,26 mcg/kg/h. Las dosis de dexmedetomidina y de agentes sedoanalgésicos de rescate no fue significativamente distinta entre los tres grupos pero la duración de la infusión de dexmedetomidina fue superior en el grupo C vs. A (p=0,03) y C vs. B (p=0,002). Los pacientes neonatales requirieron dosis de dexmedetomidina más altas (0,69 ± 0,25

vs. 0,47 ± 21 mcg/kg/h (p<0,003)). Se consiguió un patrón de sueño normal o una sedación moderada en el 94% de los casos y ausencia de dolor o dolor leve en el 90% de los casos. Los puntajes en escalas de sedación y analgesia fueron similares para los 3 tres grupos.

La presión arterial sistólica (PAS) disminuyó de 89 ± 15 a 85 ± 11 mmHg (p=0,05), la frecuencia cardíaca (FC) de 149 ± 22 a 129 ± 16 (p<0,001) y la frecuencia respiratoria (FR) permaneció sin cambios. Comparando los valores basales del equilibrio ácido base con los resultados más alterados, el pH disminuyó de 7,4 ± 0,07 a 7,37 ± 0,05 (p<0,006), PO_2 de 91 ± 67 a 66 ± 29 mmHg (p<0,005), y CO_2 aumentó de 45 ± 8 a 50 ± 12 mmHg (p<0,001). PAS, FR y valores de EAB fueron similares en los tres grupos. La FC fue superior en el grupo C vs. B (p<0,001). Los pacientes neonatales presentaron valores más bajos de FC (p<0,01), FR (p<0,003) y PAS más altos (p<0,001) que el resto de pacientes.

Conclusión:

La utilización de dexmedetomidina en neonatos y lactantes en el postoperatorio de cirugía cardiaca fue bien tolerada. Su administración consigue niveles apropiados de sedación y analgesia ya sea sola o en combinación con otros agentes sedoanalgésicos.

3.2. ARTÍCULO 2

2) ***Dexmedetomidine: Therapeutic Use for the Termination of Reentrant Supraventricular Tachycardia.*** *Congenit Heart Dis*. 2012 May 22. doi: 10.1111/j.1747-0803.2012.00669.x. [Epub ahead of print]

ORIGINAL ARTICLE

Dexmedetomidine: Therapeutic Use for the Termination of Reentrant Supraventricular Tachycardia

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ABSTRACT

Objectives. The current drug of choice for reentrant supraventricular tachycardia (SVT) is adenosine followed by verapamil or diltiazem. Although limitations and significant adverse events have been encountered over the years, an alternative effective and safe agent has not been available. Dexmedetomidine has recently been shown to have potential antiarrhythmic effects, and here we describe our experience in the acute termination of reentrant SVT.
Design. Retrospective case series.
Setting: Quaternary University Children's Hospital, Cardiac Intensive Care Unit.
Patients: Patients who received dexmedetomidine for SVT in the past 5 years.
Interventions: None.
Outcome Measures: SVT episodes terminated with dexmedetomidine were compared with episodes terminated with adenosine.
Results. Fifteen patients, median age of 10 days (6–16), were given 27 doses of dexmedetomidine, mean dose 0.7 ± 0.3 mcg/kg, for a total of 27 episodes of SVT. Successful termination occurred in 26 episodes (96%) at a median time of 30 seconds (20–35). Duration of sinus pause was 0.6 ± 0.2 seconds, there was one episode of hypotension and no bradycardia and sedation lasted for 34 ± 8 minutes. Five patients received 27 doses of adenosine, with an overall successful cardioversion in 17 patients (63%) ($P = .0017$). Transient bradycardia and hypotension was seen in three patients (11%), agitation in 16 patients (59%), and bronchospasm in one patient. Median sinus pause was 2.5 seconds (2–9) ($P < .001$).
Conclusions. Dexmedetomidine appears to have novel antiarrhythmic properties for the acute termination of reentrant SVT. Although adenosine is very effective, dexmedetomidine may prove to possess a more favorable therapeutic profile with increased effectiveness and fewer side effects.

Key Words. Dexmedetomidine; Arrhythmias; Supraventricular Tachycardia; Adenosine; Adrenergic Agonists; Cardioversion

Introduction

Reentrant supraventricular tachycardia (SVT) is a rather common cardiac emergency. Since the 1990s, adenosine has become the first-line agent for the chemical cardioversion of reentrant SVT followed by nondihydropiridine calcium channel blockers verapamil and diltiazem.[1] Although limitations and potential significant adverse events have been encountered over the years with these medications, an alternative effective agent with quick onset and an acceptable safety profile was not available for pediatric patients.

Institute where the work was conducted: Study was performed at the Cardiac Intensive Care Unit, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224.

The use of adenosine, although well tolerated in the majority of cases, can be associated with an unpredictable duration of bradycardia and asystole coupled with a rather frightening feeling of "impending doom."[5] In addition, it has an ultrashort half-life making it essentially of no use for patients with multiple recurring SVTs, an SVT recurrence rate of 9–57%, pro-arrhythmic effect with rare but potentially lethal polymorphic ventricular tachycardia, bronchospasm and a reported dose dependent efficacy between 70% and 95%.[2–5] Verapamil and diltiazem have also been associated with adverse effects, including ventricular dysfunction, hypotension, and cardiovascular collapse particularly when given in infants and neonates.[6–8]

Dexmedetomidine an alpha-2 adrenoreceptor agonist with primary sedative properties has recently been shown to have potential antiarrhythmic effects. In our previous series, dexmedetomidine was used for the acute treatment of supraventricular tachyarrhythmias and four patients with reentrant SVT were successfully cardioverted.[9] Although the current study is similar to the four patients already described previously, we strongly felt that additional description of our experience would add significantly to the rather limited body of literature. Furthermore, in a recent prospective, observational controlled study, we demonstrated that when continuous infusion of dexmedetomidine is used during the perioperative period for cardiac surgery, the incidence of ventricular and supraventricular tachyarrhythmias is decreased.[10] In this observational study, dexmedetomidine served as an agent to prevent tachyarrhythmias and was not utilized as a rescue agent to acutely treat tachyarrhythmias. Although the exact mechanism of this antiarrhythmic effect is not known, a central alpha-2 adrenoreceptor mediated enhancement of vagal neural activity appears to play a potential role.[11]

In the current study, we sought to describe our ongoing experience and provide an update regarding the use of dexmedetomidine in the termination of reentrant SVT.

Materials and Methods

This retrospective case series was approved by the University of Pittsburgh Institutional Review Board. Patients admitted to the cardiac intensive care unit (CICU) from 2006 to 2010 and who received dexmedetomidine (Hospira, Inc. Lake Forest, IL, USA) for reentrant SVT were included. None of these patients were included in previous publications.

Dexmedetomidine has been used in our institution since 2003, primarily for off-label sedation and analgesia.[12–14] In 2006, it was first used for the treatment of various types of tachyarrhythmias and, to date, more than 100 patients have been treated. With this experience, dexmedetomidine has become one of the routine, off-label agents for SVT termination. Our general decision pathway is shown in Figure 1, although the final choice of antiarrhythmic to be given remains with attending on duty.

Dexmedetomidine 0.5–1.0 mcg/kg is given as a slow intravenous push over 20 seconds followed by a 5–10 mL saline flush. Adenosine is given at the standard two-staged protocol, 0.1 mg/kg followed by 0.2 mg/kg rapid bolus over 1–2 seconds followed by 5–10 mL saline flush. Vital signs are recorded every 2 minutes and continuous telemetry and/or 12-lead electrocardiogram (ECG) is obtained during the administration. All baseline and subsequent telemetry and ECG recordings are reviewed by a cardiac intensivist and an electrophysiologist. Following administration of dexmedetomidine, vital signs and sedation levels using an institutional 0–3 ICU sedation scale (0; none, 1; mild, 2; moderate, 3; severe sedation) are recorded every 5 minutes until recovery. Presence of agitation was taken from the nursing documentation reports.

Exclusion criteria for the use of dexmedetomidine include anaphylaxis to alpha-2 agonists, prematurity less than 32 weeks gestational age, recent history of complete atrioventricular (AV) block in absence of a pacemaker and hemodynamic instability.

Based on our experience and to avoid bias of possible spontaneous recovery to normal sinus rhythm (NSR), successful response is considered if cardioversion occurs in less than 3 minutes. This cutoff was chosen after reviewing our results and not a priori. Dexmedetomidine has a distribution half-life of 6 minutes, so a longer period of time could be granted to the successful termination of SVT. Nevertheless, given the possibility of spontaneous termination of SVT, decreasing the cutoff time would increase the odds that SVT termination is because of dexmedetomidine.

If the study group received adenosine at any point during the CICU stay, the response and hemodynamic data during the adenosine administration were also analyzed. The children who

Figure 1. Algorithm for the treatment of supraventricular tachycardia. NSR, normal sinus rhythm.

received adenosine were a subset of the group who received dexmedetomidine.

Statistical Analysis

For statistical analysis, data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive summaries are presented as counts and proportions for categorical variables, and mean ± standard deviation or median with interquartile range (IQR) for continuous variables where appropriate. The Fisher's exact test was used to compare the duration of sinus pause and the duration of NSR between patients receiving dexmedetomidine and those receiving adenosine.

Results

Fifteen patients with a median age of 10 days (IQR 6–16) were given 27 doses of dexmedetomidine for a total of 27 episodes of SVT. Fourteen patients were neonates, one patient was 2 months old and another one was 2 years old. Five patients (33%) had more than one episode of SVT. Table 1 summarizes the characteristics of the patients and SVT episodes.

Nine patients (60%) had congenital heart disease. Six of these went on to have cardiac surgery and one had cardiac catheterization. Among the 6 postoperative patients, the episode of SVT occurred at a median of 1 day (IQR 1–9 days) after the procedure. None of these patients were receiving dexmedetomidine infusion at the time of the SVT episodes.

Among the 27 episodes treated with dexmedetomidine, reentrant SVT was successfully terminated in 26 episodes (96%) (Table 1). Examples of this cardioversion are shown in Figures 2 and 3. For the one unsuccessful episode, the patient had received 0.5 mcg/kg of dexmedetomidine and termination of SVT occurred 5 minutes after the administration, which was outside our study criteria of dexmedetomidine-related success.

Four patients developed 12 episodes of SVT *prior* to the first administration of dexmedetomidine (mostly during interhospital transportation)

Table 1. Characteristics of Patients and Supraventricular Tachycardia

	Dexmedetomidine	Adenosine†
Patients, n	15	4
Age, days	10 (6–16)‡	10 (6–11)‡
Episodes of supraventricular tachycardia, n	27	22
Preexcitation Wolf–Parkinson–White syndrome, n (%)	3 (20)	1 (25)
Cardioversion to normal sinus rhythm, n (%)	26 (96)	17 (77)
Dexmedetomidine dose, mcg/kg	0.7 ± 0.3	
Supraventricular tachycardia rate, bpm	234 ± 22	235 ± 16
Time to normal sinus rhythm, s	30 (20–34)‡	8 ± 3
Heart rate after cardioversion, bpm	126 ± 22	98 ± 23
Duration of sinus pause after cardioversion, s	0.6 (0.5–0.8)‡	2.5 (2–9)‡
Duration of normal sinus rhythm between episodes of SVT*	4 (1–10.5)‡ h	2 (0.3–4)‡ min

*Includes only the five patients with recurrent SVT episodes.
†The children who received adenosine were a subset of the group who received dexmedetomidine.
‡Data represent median with interquartile range.

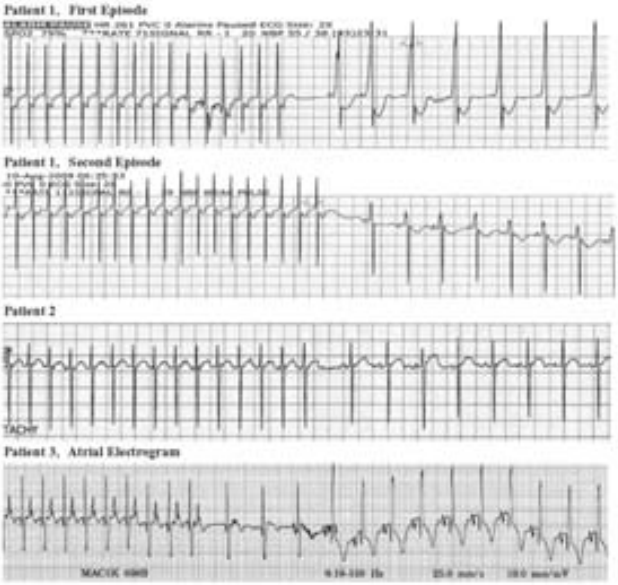

Figure 2. Episodes of supraventricular tachycardia termination after dexmedetomidine.

and 10 episodes *after* dexmedetomidine (over the span of several days). Eight episodes responded immediately to 0.1 mg/kg of adenosine and additional nine episodes were terminated with 0.2 mg/kg. The total successful termination rate for adenosine was 77%. Of these four patients, two patients had no congenital heart disease, one patient had Norwood procedure and one patient had aortic valve stenosis.

Four patients from this cohort had multiple episodes of SVT. A total of 22 episodes (including SVT episodes that occurred during interhospital

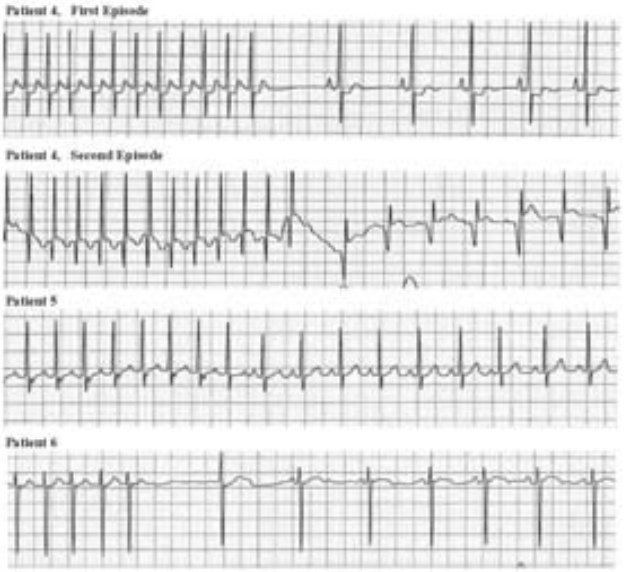

Figure 3. Additional episodes of supraventricular tachycardia termination after dexmedetomidine.

transport) were recorded. Adenosine was successful in terminating 17 of these episodes (77%) with either 0.1 mg/kg (six episodes) and 0.2 mg/kg (nine episodes).

Among the five patients with recurrent SVT, the median duration of NSR between SVT episodes was 2 minutes (IQR 20 seconds–4 minutes) after adenosine and 4 hours (IQR 1–10.5 hours) after dexmedetomidine ($P = .001$).

The sedative effect of dexmedetomidine was observed in all patients. The median level of sedation was 1.9 (IQR 1–2). None of the patients was in a deep level of sedation. The recovery time from sedation was 34 ± 8 minutes. Patients were intubated for 14 (54%) of the dexmedetomidine doses.

Adverse Events with Dexmedetomidine

None of the patients developed any bradycardia. The minimum heart rate was 88 bpm and lasted for less than 5 minutes. Hypotension (mean blood pressure 34 mm Hg) was seen in one occasion, in a 7-day-old patient, and was given 2 mcg/kg phenylephrine. Hypertension above the 95th percentile for age was seen in four occasions (15%). The maximum systolic blood pressure was 115 mm Hg and was seen in a 27-month-old patient. The other three episodes were 95 mm Hg, 98 mm Hg, and 105 mm Hg. All hypertensive episodes lasted less than 2 minutes and resolved without intervention. There were no new tachyarrhythmias, agitation, bronchospasm, or respiratory depression.

Adverse Events with Adenosine

Among the four patients who received a total of 27 doses of adenosine, bradycardia was observed after three (11%) of these doses. The lowest heart rate was 57 bpm, associated with hypotension (mean blood pressure 29 mm Hg) lasting for 2 minutes and was observed in a 6-day-old patient. The median sinus pause was significantly longer when compared with dexmedetomidine, 2.5 (IQR 2–9) vs. 0.6 (IQR 0.5–0.8) seconds ($P < .001$) (Figure 4).

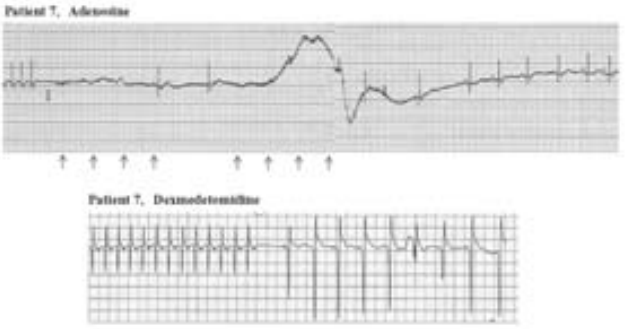

Figure 4. Termination of supraventricular tachycardia after adenosine (upper tracing) and after dexmedetomidine (lower tracing). Note the significant difference in the postcardioversion duration of asystole (arrows represent 1-second duration gaps).

Transient agitation that lasted seconds was common and was seen after 16 doses (59%). Bronchospasm was seen in one patient. None of the adenosine adverse events required intervention.

Four of the 15 patients (27%) were on existing antiarrhythmic medications at the time of the first dexmedetomidine administration. These included amiodarone, propranolol, digoxin, procainamide, and flecainide. Two of these patients were on more than one antiarrhythmic agent. Twelve patients (80%) were discharged home on antiarrhythmic medications including propranolol, digoxin, amiodarone, and sotalol. Three remained on more than one agent. Three patients did not remain on any antiarrhythmics because the SVT was deemed to be "transient" and related only to the postoperative course. The total CICU length of stay was 5 days (IQR 2–10).

Discussion

The results of the present study support our previous initial experience and demonstrate that the use of dexmedetomidine for the termination of reentrant SVT is associated with a high rate of success and an acceptable adverse effect profile.[9] In the recent "2010 Pediatric Basic and Advanced Life Support International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations," the results of our previous study have been acknowledged, but the committee stated the "knowledge gap" that exists with the use of dexmedetomidine in the treatment of SVT.[11] We hope that this larger report would narrow that gap until results from a proper prospective control trial become available.

Efficacy

Success with dexmedetomidine was impressive with 96% termination of SVT. The mean dexmedetomidine loading dose used was 0.7 mcg/kg with a maximum dose of 1 mcg/kg. This dosage is within the range recommended by the manufacturer for adults and within the range used in children for sedation in our institution.[10] Although the adenosine success rate was lower than expected, it was not outside the 60–95% range reported in the literature.[7,16] Due to adenosine's ultra short duration of action, cardioversion with immediate recurrence of the SVT is likely and perhaps justifiably reported as failure by many. Furthermore, in our current study, none of the patients received multiple, sequential 0.2 mg/kg doses after the first dose of dexmedetomidine. If no cardioversion occurred after one 0.2 mg/kg dose of adenosine patients were then given dexmedetomidine. These factors perhaps had contributed to the overall decreased success of adenosine.

The antiarrhythmic mechanism of dexmedetomidine-induced SVT cardioversion is not completely understood, and to date, no electrophysiologic studies have been performed to assess this effect. What we do know however and base our hypothesis on is the fact that the autonomic nervous system plays an important role in

the genesis and maintenance of arrhythmias and of reentrant SVT in particular. We also know that AV nodal tissue has an abundance of autonomic innervation, with both parasympathetic—vagal fibers and sympathetic thoracic—spinal fibers. Therefore, dexmedetomidine, an alpha-2 adrenoreceptor agonist with both sympatholytic and parasympathomimetic properties, is perhaps an ideal agent for an AV nodal-dependent reentrant SVT. The dorsal motor nucleus of the vagus nerve is an important region where an efferent parasympathetic nerve originates, and the activity of this region is directly regulated by the nucleus of tractus solitarius, where an afferent vagal sensory input terminates.[11,17,18] Both of these nuclei are rich in alpha-2 adrenoreceptors, and their activation by dexmedetomidine could lead to a potent enhancement of vagal activity resulting in sufficient slowing of the AV nodal conduction for termination of the SVT. Although in a previous study of ours we failed to show any prolongation of the heart rate-adjusted PR interval, those measurements were performed while on a "steady" level continuous infusion of dexmedetomidine and not after a loading dose.[19] It is possible that the AV nodal conduction is depressed in the phase of a high peak plasma concentration of dexmedetomidine. A small but well-performed electrophysiologic study by Hammer et al. did show that after a 1 mcg/kg loading dose, the AV nodal function was depressed, as evidenced by increased AV nodal block cycle lengths and effective refractory period.[20] Furthermore, in this current study, there was strong evidence that dexmedetomidine acts on the AV node. In several of the ECG tracings where "p" waves were discernible (Figure 2: Patients 1 and 3; Figure 3: Patient 5; and Figure 4: Patient 7), SVT appeared to terminate with a retrograde "p" wave. This indicates a block at the anterograde limb of the reentrant loop where the AV node is and an intact retrograde limb where the accessory pathway is.

An additional benefit of this dexmedetomidine-based approach is the duration of its effect. Based on the current results, the earliest recurrence of an SVT episode after dexmedetomidine was 1 hour. This effect helps to increase the amount of arrhythmia-free time and thus hemodynamic stability and decrease the amount of multiple administrations of adenosine until a longer acting agent of choice, e.g., digoxin and amiodarone, has reached an effective, steady level. An example of this beneficial effect was seen in one of the current study patients who was administered nine doses of adenosine over a period of 1 hour while en route to the hospital vs. three doses of dexmedetomidine over 9 hours while in the CICU until his digoxin loading dose reached a therapeutic level.

Safety

Perhaps the most important finding is the fact that dexmedetomidine-induced cardioversion occurred without any significant postcardioversion sinus pause or asystole. In Figure 4, a classic example of dexmedetomidine vs. adenosine cardioversion is demonstrated. The SVT episodes are from the same patient at different points in time. During the first episode, the patient was given adenosine with termination of SVT followed by transient asystole of 4 seconds, interrupted by two atrial beats and followed by an additional 4.5-second asystole. At a separate episode, patient was given dexmedetomidine, and the SVT was terminated without any significant postcardioversion pause. This is of paramount importance as prolonged sinus pause, seen quite commonly with adenosine, is associated with the rather frightening feeling of "impending doom."[7]

Due to dexmedetomidine's sedative and anxiolytic properties, agitation was not observed in any patient. Mild to moderate sedation was observed in all patients, an effect that lasted just over half an hour. Although dexmedetomidine lacks or has minimal negative effects on the respiratory drive, it should still be administered under the supervision of personnel with airway management skills.

In comparison with adenosine's bronchospastic side effects, dexmedetomidine has bronchodilatory properties, and thus it is not contraindicated during asthma attacks where the administration of multiple airway sympathomimetic agents puts susceptible patients at risk for SVT.

In addition to the above properties dexmedetomidine appears to lack any pro-tachyarrhythmic side effects. To the contrary, as described earlier, we have used it for various types of tachyarrhythmias.[9,21] Adenosine on the other hand, because it shortens the atrial action potential duration, it can facilitate the initiation of atrial fibrillation and in the presence of an accessory pathway, e.g., Wolf–Parkinson–White syndrome, it can promote life-threatening ventricular fibrillation.[22]

Limitations

The current study is limited by its retrospective nature and the small number of patients. As a control group, we used the episodes treated with adenosine from the same patients and although it could be considered a bias at the same time, it

avoids patient and arrhythmia variability. Several of the dexmedetomidine doses were given in the presence of other antiarrhythmic agents, and thus a synergistic or additive effect is possible. This study has served as our pilot study, and currently a prospective control study of dexmedetomidine vs. adenosine is under way.

Conclusion

Dexmedetomidine appears to have novel antiarrhythmic properties for the acute termination of AV nodal-dependent reentrant SVT. Although adenosine, the current drug of choice, is very effective, dexmedetomidine may prove to possess a more favorable therapeutic profile with increased effectiveness, lack of asystole and the feeling of "impending doom," longer duration of action for the patient with multiple episodes, an anxiolytic effect for the patient in distress, no pro-tachyarrhythmic effect, and no negative inotropic effect.

Author Contributions

Dr. Chrysostomou: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, and statistics.

Drs. Morell, Wearden, Jooste, Beerman: concept/design, critical revision of article, and approval of article.

Dr. Sanchez de Toledo: concept/design, critical revision of article, approval of article, and data Collection.

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Conflict of interest: Dr. Chrysostomou has previously received research support from Hospira Inc.

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Objetivo:

describir la experiencia con la utilización de dexmedetomidina en el tratamiento de la taquicardia paroxística supraventricular (TPSV)

Diseño:

Estudio retrospectivo de serie de casos.

Población:

Pacientes pediátricos que recibieron dexmedetomidina para la finalización de TPSV

Periodo: 2006-2010

Variable resultado:

Episodios de TPSV finalizados con dexmedetomidina comparados con episodios de dexmedetomidina finalizados con adenosina en el mismo periodo de estudio.

Resultados:

15 pacientes con edades media de 10 días (6días-16meses) recibieron 27 dosis de dexmedetomidina, con dosis media de 0,7±0,3 mcg/kg para un total de 27 episodios de TPSV. Se consiguió finalizar satisfactoriamente el episodio de TPSV en 26 ocasiones (96%) con un tiempo medio de 30 segundos (20-35 seg). La duración de la pausa sinusal fue de 0,6 ± 0,2 segundos. Se documentó un episodio de hipotensión, no se registró bradicardia y la sedación se prolongó 34±8 minutos. En el mismo periodo de tiempo, 5 pacientes recibieron 27 dosis de adenosina consiguiendo finalizar 17 de los 27 (63%) episodios de TPSV. En ellos se registró bradicardia y hipotensión en 3 pacientes (11%), agitación en 16 (59%) y broncoespasmo en uno. El tiempo medio de pausa sinusal fue de 2,5 segundos (2-9 seg).

Conclusión:

Dexmedetomidina parece poseer propiedades antiarritmogénicas útiles para la finalización de episodios de TPSV. A pesar de que la adenosina es altamente eficaz, dexmedetomidina parece disponer de un perfil más favorable con una eficacia superior y menor incidencia de efectos adversos.

3.3. ANEXO-1 (ARTÍCULO 3)

3) **Perioperative Use of Dexmedetomidine Is Associated With Decreased Incidence of Ventricular and Supraventricular Tachyarrhythmias After Congenital Cardiac Operations.** *Ann Thorac Surg*. 2011; Sep;92(3):964 –72

PEDIATRIC CARDIAC

Perioperative Use of Dexmedetomidine Is Associated With Decreased Incidence of Ventricular and Supraventricular Tachyarrhythmias After Congenital Cardiac Operations

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Background. Postoperative tachyarrhythmias remain a common complication after congenital cardiac operations. Dexmedetomidine (DEX), an α-2 adrenoreceptor agonist, can have a therapeutic role in supraventricular tachyarrhythmias for cardioversion to sinus rhythm or heart rate control. Whether routine perioperative use of DEX decreases the incidence of supraventricular and ventricular tachyarrhythmias was studied.

Methods. In this prospective cohort study, 32 pediatric patients undergoing cardiothoracic operations received DEX and were compared with 20 control patients who did not receive DEX.

Results. Dexmedetomidine was started after anesthesia induction and continued intraoperatively and postoperatively for 38 ± 4 hours (mean dose, 0.76 ± 0.04 μg/kg/h). Ten control patients and 2 DEX patients sustained 16 episodes of tachyarrhythmias ($p = 0.001$), including a 25% vs 0% ($p = 0.01$) incidence of ventricular tachycardia and 25% vs 6% ($p = 0.05$) of supraventricular arrhythmias in the control and DEX group, respectively. Transient complete heart block occurred in 2 control patients and in 1 DEX patient. Control patients had a higher heart rate (141 ± 5 vs 127 ± 3 beats/min, $p = 0.03$), more sinus tachycardia episodes (40% vs 6%; $p = 0.008$), required more antihypertensive drugs with nitroprusside (20 ± 7 vs 4 ± 1 μg/kg; $p = 0.004$) and nicardipine (13 ± 5 vs 2 ± 1 μg/kg; $p = 0.02$), and required more fentanyl (39 ± 8 vs 19 ± 3 μg/kg; $p = 0.005$).

Conclusions. Perioperative use of dexmedetomidine is associated with a significantly decreased incidence of ventricular and supraventricular tachyarrhythmias, without significant adverse effects.

(Ann Thorac Surg 2011;92:964–72)

Postoperative tachyarrhythmias remain a common complication after congenital cardiac operations, with an incidence between 25% and 50% [1, 2]. Factors that have been associated with an increased risk for these arrhythmias include preexisting myocardial dysfunction, a complex operation associated with myocyte damage and edema, extensive suture lines, myocardial ischemia, postoperative electrolyte disturbances, and cardiopulmonary bypass (CPB)-related inflammatory response and catecholamine surge.

These arrhythmias can jeopardize hemodynamic stability, and urgent treatment may often be necessary to slow the heart rate (HR) or restore normal sinus rhythm (NSR). A number of studies have examined the efficacy of prophylactic treatment for the prevention of postoperative arrhythmias, particularly in adults [3–6]. Prophylaxis with β-blockers appears to have a benefit in a subset of supraventricular arrhythmias; however, the use of these agents has been avoided after pediatric cardiac operations largely because of the negative inotropy. Digoxin and magnesium have had equivocal results. Although some studies have shown that amiodarone is more effective, particularly for atrial fibrillation, others have failed to do so. Furthermore, amiodarone has a serious adverse-effect profile, including bradycardia, hypotension, heart block, and negative inotropy, that likely

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outweighs its potential benefit. Many consider the routine use of amiodarone excessive and not warranted in the pediatric population.

Dexmedetomidine, a highly selective α-2 adrenoreceptor agonist, is one of the latest sedative and analgesic agents that has earned a place in the armamentarium of anesthesiologists and intensivists, partly because of its minimal effect on respiration. Beyond its well-known properties, a recent study has shown that dexmedetomidine has potential antiarrhythmic properties and can be used for the acute treatment of pediatric supraventricular tachyarrhythmias, including junctional ectopic, atrial ectopic, and reentrant type tachycardias [7]. In addition, animal studies have demonstrated that activation of imidazoline and α-2 adrenoceptors in the central nervous system prevents adrenaline-induced ventricular tachycardia and that stimulation of the vagus nerve may be critical for this antiarrhythmic effect [8–11]. With this background, we hypothesized that administration of dexmedetomidine during the perioperative period of children undergoing cardiothoracic operations would be associated with decreased incidence of supraventricular and ventricular arrhythmias.

Material and Methods

This was a prospective cohort study of pediatric patients undergoing cardiothoracic operations with CPB who were enrolled from October 15, 2009, to June 30, 2010. Patients were divided into two groups according to the anesthetic technique used: patients who were initiated on dexmedetomidine (Hospira Inc, Lake Forest, IL) infusion after anesthesia induction comprised the dexmedetomidine group (DEX group), and patients who did not receive dexmedetomidine as part of their anesthetic regimen comprised the control group. The decision whether patients would receive dexmedetomidine was a clinical decision and based entirely on the preference of the primary cardiac anesthesiologist.

The primary outcome was the incidence of postoperative supraventricular and ventricular tachyarrhythmias. Supraventricular tachyarrhythmias included reentrant supraventricular tachycardia (SVT), atrial ectopic tachycardia (AET), atrial flutter, atrial fibrillation, sustained atrial bigeminy, and junctional ectopic tachycardia (JET). Ventricular tachyarrhythmias included ventricular tachycardia (VTAC), ventricular fibrillation, and sustained or prolonged ventricular ectopy. Secondary outcomes included duration of mechanical ventilation, inotropic and vasotropic support, cardiac intensive care unit and hospital length of stay, and perioperative mortality.

To ensure consistency in the surgical, anesthetic, and postoperative approach during the study period, the medical team remained the same, including the cardiothoracic surgeons, cardiac anesthesiologists, and cardiac intensivists. The study was approved by the local Institutional Review Board, and an informed consent was obtained from all patients' legal guardians. A designated data and safety monitoring person reviewed the results every 3 months.

Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria as obtained from a review of medical records: significant baseline neurologic impairment that prohibited accurate titration of sedative and analgesic agents, weight less than 2 kg, permanent pacemaker, arrhythmias within the last 6 months, antiarrhythmic medications and β-blockers within the last 72 hours, and use of amiodarone or dexmedetomidine within the last 30 days. Additional exclusion criteria included use of dexmedetomidine for 12 hours or less after the end of CPB and use of dexmedetomidine for sedation in the control group in excess of 1 μg/kg/d because 1 μg/kg intravenous load is the recommended dose by the manufacturer to reach steady state. If dexmedetomidine was used in the control group as a rescue agent for arrhythmia and the dose exceeded 1 μg/kg/d, then all recorded data after the initiation of dexmedetomidine were also excluded from analysis. Dexmedetomidine is currently considered part of the standards of care for the treatment of supraventricular tachyarrhythmias in our center.

Anesthetic Technique

INTRAOPERATIVE. The anesthetic management followed preestablished guidelines. Anesthesia was induced with sevoflurane or intravenous fentanyl in unstable patients. Rocuronium was used for muscle relaxation. Patients were maintained on isoflurane (end-tidal, 0.5% to 1.6%) and a sufentanil infusion (0.2 to 0.3 μg/kg/h). Some patients received a caudal block consisting of 0.25% bupivacaine (1 to 1.5 mL/kg) with epinephrine (1:200000) and preservative-free morphine (40 μg/kg). In the DEX group, dexmedetomidine was administered before the surgical incision as loading dose (1 μg/kg), followed by an hourly infusion (0.5 μg/kg) that was continued through the operation and to the cardiac intensive care unit. Intraoperative opioids were minimized in an effort to extubate potential patients before leaving the operating room. In extubated patients, additional dexmedetomidine, midazolam, and fentanyl were titrated to patient comfort. In patients who would remain intubated, anesthesia was further supplemented with fentanyl (10 to 30 μg/kg).

POSTOPERATIVE. Patients in the DEX group continued to receive the dexmedetomidine infusion as the main sedative and analgesic agent at an hourly dose of 0.1 to 1.5 μg/kg. Adjustments in the dexmedetomidine dose and in the administration of other rescue sedative and analgesic agents were made according to standard cardiac intensive care unit sedation and analgesia scales. For breakthrough agitation or pain, or both, the dexmedetomidine infusion was increased by 0.1 to 0.3 μg/kg/h. If this was inadequate 20 minutes after the change, a rescue agent was administered, and the dexmedetomidine infusion was further increased to a maximum of 1.5 μg/kg/h. If at the maximum dexmedetomidine dose the patient still required frequent rescue doses (> 1 dose/h), then a fentanyl infusion (range, 0.5 to 2 μg/kg/h) was started. The intermittent rescue agents included intravenous fentanyl (1 μg/kg), morphine (0.05 mg/kg), midazolam (0.1

mg/kg), and lorazepam (0.1 mg/kg) every hour as needed, and enteral chloral hydrate (15 mg/kg) every 4 hours as needed. Muscle relaxation was provided with cisatracurium as necessary.

Control patients were maintained on a fentanyl infusion (1 to 4 μg/kg/h) if intubated and subsequently; if not intubated, they were administered the same rescue sedatives and analgesics used for the DEX group, using the same indicators.

CPB Management

Anticoagulation was initiated with heparin (350 to 400 U/kg) with the target kaolin-activated coagulation time (HEMOCHRON Jr. Signature Microcoagulation System, International Technidyne Corp, Edison, NJ) value of 450 seconds or higher before CPB began. Nonpulsatile CPB was performed with roller pump and a microporous hollow-fiber membrane oxygenator. Pump flow rates ranged from 3.0 to 3.2 L/min/m^2 for temperatures of 37°C to 30°C and from 2.0 to 2.5 L/min/m^2 for temperatures of 29.9°C to 18°C. Magnesium sulphate (0.4 mEq/kg) and methylprednisolone (30 mg/kg) were added to the pump prime. A pH-stat acid-base management strategy for patients undergoing deep hypothermic circulatory arrest was used without the addition of any continuous regional low-flow perfusion.

For inotropic support, epinephrine (0.02 to 0.1 μg/kg/min) and milrinone (0.5 to 1.2 μg/kg/min) were routinely used to facilitate weaning from CPB. For control of hypertension, sodium nitroprusside (0.5 to 3 μg/kg/min) was used as needed.

Modified ultrafiltration was performed after termination of CPB in all patients who weighed less than 15 kg, ultrafiltrating a volume of 30 to 100 mL/kg, up to a maximum of 600 mL. Furosemide (1 mg/kg) was administered up to a 20-mg maximum to all patients after CPB was terminated. Protamine (4 mg/kg) was given for reversal of heparin after termination of CPB and the modified ultrafiltration.

Arrhythmia Diagnosis and Definition

All patients were monitored using full-disclosure telemetry (CIC Pro-v5.0.3, GE Medical Systems Information Technologies, Inc, Milwaukee, WI) that stores information up to 48 hours. The telemetry tracings were reviewed manually every 12 to 24 hours, and documented arrhythmias were printed and stored. In addition, a 12-lead electrocardiogram (ECG) and an atrial electrogram were obtained when possible. A second cardiologist, blinded to the groups, independently reviewed all arrhythmia recordings. Arrhythmias during CPB or during separation from CPB were not considered significant and were excluded from analysis.

JUNCTIONAL ECTOPIC TACHYCARDIA. (1) a HR exceeding 170 beats/min with a QRS morphology similar to the baseline QRS; (2) atrioventricular (AV) dissociation, with the ventricular rate equal or higher than the atrial rate; (3) ventriculoatrial (VA) association with retrograde 1:1 or Wenckebach conduction; (4) a pattern of "warm-up" phenomenon at initiation, although not necessary, and (5) arrhythmia duration of 5 minutes or longer, or associated hemodynamic instability. In cases of 1:1 VA conduction, short VA interval, and no obvious P waves, or where tachycardia onset was abrupt, attempts were made to exclude a reentrant-type mechanism. An arrhythmia that met the above criteria but with a HR of 170 beats/min or less was classified as a junctional accelerated rhythm.

ATRIAL ECTOPIC TACHYCARDIA. Different P-wave morphology than the sinus P wave, HR of 150 to 250 beats/min with substantial variability, typically a "warm-up" phenomenon, although not necessary, and duration of arrhythmia of 5 minutes or more or associated hemodynamic instability.

ATRIAL FLUTTER. Abrupt onset tachyarrhythmia with no distinct P waves but rather typical flutter waves, HR of 150 to 350 beats/min, variable AV block, or 1:1 AV conduction with QRS morphology similar to baseline, duration of arrhythmia of 5 minutes or more, and associated hemodynamic instability.

ATRIAL FIBRILLATION. Abrupt-onset irregular tachyarrhythmia, with irregular ventricular response without distinct P waves but rather a ripple of chaotic atrial depolarization, HR of 150 to 350 beats/min and duration of arrhythmia of 5 minutes or more, and associated hemodynamic instability.

REENTRANT SVT. Abrupt-onset regular tachycardia with QRS morphology similar to baseline and HR of 200 to 350 beats/min, atrial electrogram may show retrograde P waves with a short VA interval, a duration of arrhythmia of 3 minutes or longer, or associated hemodynamic instability. In this type of arrhythmia, the 3-minute duration was chosen because of the historical propensity of the clinical team to intervene and attempt cardioversion.

VENTRICULAR TACHYCARDIA. Abrupt-onset regular tachycardia with wide QRS morphology different from baseline and a HR of 150 to 350 beats/min and duration of 10 beats or longer.

VENTRICULAR FIBRILLATION. Abrupt-onset irregular tachycardia without discernible P waves or QRS complexes but rather a ripple of chaotic ventricular depolarization.

OTHER ARRHYTHMIAS. Sustained atrial or ventricular contractions of 30 or more per minute for 30 minutes or longer.

Risk Stratification

To ensure similar group comparison, the basic Aristotle score was used to risk-stratified patients by the complexity of their surgical procedures [12]. The basic Aristotle score adjusts for the complexity of the procedures derived from three factors: the potential for death, the potential for morbidity, and the anticipated technical difficulty.

Postoperative Monitoring

The following variables were monitored for up to 72 hours after the end of CPB: vital signs, duration of mechanical ventilation, requirement of sedatives, analge-

Ann Thorac Surg
2011;92:964–72

sics, inotropic, and systemic vasodilator support, and use of antiarrhythmic medications. Laboratory monitoring included immediately after CPB and then daily creatinine, potassium, magnesium, and ionized calcium levels, and every 4 hours lactate and blood gases with electrolytes, as clinically indicated. Episodes of sinus tachycardia and hypertension (defined as values ≥ 90% for age) and sinus bradycardia and hypotension (values ≤ 5% for age, or bradycardia requiring temporary atrial pacing) were recorded for analysis.

Statistics

On the basis of an incidence of all arrhythmias after pediatric cardiac operations of 15% to 48%, and assuming an incidence of the primary end point of 30% in the control group and a 50% reduction in the DEX group, we calculated that 52 patients would establish a power of 95% based on a two-tailed α error of 0.05 [1, 2].

Descriptive summaries during the 72-hour period are presented as counts (%) for categoric variables, and means ± standard error or median (range) for continuous variables. For the primary end point of postsurgical tachyarrhythmia, the difference in the proportions between the treated and control arm was tested using the χ^2 test. For the comparison of demographics, operative details, postoperative medication use, and length of stay, the two study arms were compared using the χ^2 test for categoric variables. The parametric independent-samples *t* test and nonparametric Mann-Whitney *U* test were used for continuous variables that did or did not meet the assumption of normality, respectively. Repeated measures ANOVA with the Fisher least significant differences post hoc analysis was used to compare the time-varying vital signs. The Pearson correlation coefficient was used to measure the correlation between incidence of tachyarrhythmias and the use of epinephrine. All statistical comparisons were performed as two-sided tests with a significance level of 0.05 using SPSS 17.0 software (SPSS Inc, Chicago, IL).

Results

After interim analysis, a significant difference was observed between the groups, with a statistically higher incidence of tachyarrhythmias in the control group. In addition, given the nature of the study design (noeblinded cohort study), a shift in clinical practice occurred from an approximate use of dexmedetomidine in about 60% of patients (based on the previous 2 years of hospital data) to more than 95%. This shift in practice occurred because of the observation of less tachyarrhythmia in the DEX group and made the continuation of the study almost impossible given the lack of an adequate number of control patients. The study was terminated after enrollment of 52 patients.

The patient baseline characteristics and intraoperative variables are summarized in Table 1. There were no

Table 1. Demographic and Intraoperative Patient Characteristics

Variable*	Control (n = 20)	DEX (n = 32)	*p* Value
Age, mon	2.6 (0.13–158)	4.8 (0.16–198)	0.29
Weight, kg	3.9 (2.6–99)	5.3 (2.6–83)	0.23
Female sex	12 (60)	11 (34)	0.13
Aristotle score	7.3 (4.0–14.5)	8.5 (3.0–14.5)	0.24
Length of stay, day			
CICU stay[b]	4 (1–16)	4 (1–20)	0.59
Hospital stay[c]	7 (3–19)	8 (3–45)	0.63
Intraoperative data			
CPB time, min	79 ± 9	93 ± 7	0.12
Aortic clamp time, min	30 ± 6	33 ± 6	0.84
Circulatory arrest time, min	31 ± 6	26 ± 4	0.57
Modified ultrafiltration, mL/kg	71 ± 5	65 ± 3	0.14
Dexmedetomidine LD, μg/kg	...	1 ± 0.1	...
Dexmedetomidine, μg/kg/h	...	0.5	...
Sufentanil, μg/kg/min	0.33 ± 0.06	0.28 ± 0.03	0.40
Fentanyl, μg/kg	25 ± 7	20 ± 4	0.85
Midazolam, mg/kg	0.33 ± 0.06	0.33 ± 0.05	0.69
Caudal block,	2 (10)	6 (19)	0.65
Epinephrine, μg/kg/min	0.06 ± 0.01	0.07 ± 0.01	0.92
Milrinone, μg/kg/min	0.88 ± 0.17	0.87 ± 0.17	0.85
Methylprednisolone, mg/kg	28 ± 1	29 ± 1	0.4
Magnesium sulphate, mEq/kg	0.4 ± 0.1	0.4 ± 0.1	0.4

* Continuous data are presented as median (range) and mean ± standard error; categoric data are presented as number (%). [b] Length of stay from operation to CICU discharge. [c] Length of stay from operation to hospital discharge.

CICU = cardiac intensive care unit; CPB = cardiopulmonary bypass; DEX = dexmedetomidine; LD = loading dose.

differences between DEX and control groups. Seven patients in the control group (35%) and 12 in the DEX group (37%) had the highest surgical complexity of Aristotle level of 4 or basic Aristotle score of 10 to 15. Table 2 reports the surgical procedures performed in both groups. A caudal block was administered in 8 patients, 2 in the control and 6 in the DEX group ($p = 0.65$).

Two patients in the control group received dexmedetomidine during the study period. The first patient received dexmedetomidine as a rescue treatment for AET. This patient had already received amiodarone but continued having frequent episodes of EAT with HR exceeding 200 beats/min. A loading dose (1 μg/kg), followed by an infusion (1 μg/kg/h) was administered, with a significant decrease in the AET rate to less than 150 beats/min. This patient was excluded from all postoperative data analysis other than the arrhythmia analysis. The second patient received a 1-μg/kg bolus of dexmedetomidine on the first and second postoperative days for JET. The patient had only partial benefit from amiodarone and continued to have breakthrough episodes of JET, with a rate exceeding 170 beats/min. With each dose of dexmedetomidine, the JET rate decreased from 193 to 162 beats/min and from 183 to 169 beats/min, respectively.

Table 2. Cardiac Operations Performed Based on the Aristotle Classification

Classification	Control (n = 20)	DEX (n = 32)
Anomalous systemic venous connection repair	...	1
Aortic arch repair	1	1
Aortic arch repair + VSD repair	3	1
Aortic stenosis, Subvalvar, Repair	...	1
ASO	...	1
Atrial septal defect repair, Patch	...	2
AVSD, Complete, Repair	1	2
AVSD, Partial, Repair	1	...
Cardiac tumor resection	1	...
Coarctation repair, End to End, Extended	...	1
Congenitally corrected TGA repair, Atrial switch, and ASO	...	1
Cor triatriatum repair	1	...
Damus-Kaye-Stansel procedure	...	1
DORV, Intraventricular tunnel repair	...	1
Fontan, External conduit, Fenestrated	...	1
Glenn anastomosis	1	1
Norwood procedure	2	4
Pulmonary Atresia-VSD-MAPCA (pseudotruncus) repair	...	1
Rastelli	1	1
Right ventricular outflow tract procedure	1	...
TAPVC repair	1	...
TOF repair, No ventriculotomy	...	2
TOF repair, Right ventricle–pulmonary artery conduit	...	1
TOF repair, Ventriculotomy, Transannular patch	...	2
Truncus arteriosus repair	1	1
Valve replacement, Aortic or mitral, Mechanical	1	1
Valvuloplasty, Aortic or Mitral	...	2
VSD repair, Patch	4	2

ASO = arterial switch operation; AVSD = atrioventricular septal defect; DEX = dexmedetomidine; DORV = double-outlet ventricle; MAPCA = multiple aortopulmonary collaterals; TAPVC = total anomalous pulmonary venous connection; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

The DEX group received dexmedetomidine infusion for 38 ± 4 hours at a mean dose of 0.76 ± 0.04 μg/kg/h. During the 72-hour period, 20 episodes of arrhythmia were documented in 6 patients (31%): 16 tachyarrhythmias, and 4 bradyarrhythmias (Table 3). The incidence was 25% vs 0% ($p = 0.01$) for ventricular arrhythmias and 25% vs 6% ($p = 0.05$) for supraventricular arrhythmias in the control and DEX groups, respectively. Ventricular tachycardia occurred in patients after aortic arch and ventricular septal defect (VSD) repair in 2, Rastelli in 1, VSD closure in 1, truncus arteriosus repair in 1, and Norwood procedure in 1. AET occurred in 1 patient each after aortic arch and VSD repair, Norwood procedure, and right ventricular outflow reconstruction. JET occurred after VSD repair and vascular ring repair in 1 patient each. Reentrant SVT occurred after Norwood in 2 and after truncus arteriosus repair in 1. Atrial bigeminy occurred in 1 patient after Norwood repair. Junctional accelerated rhythm occurred after an atrial septal defect repair in 1. For the bradyarrhythmias, complete AV block occurred after a double-switch procedure for congenitally corrected transposition of the great arteries, after an intraventricular tunnel repair, and after a VSD closure in 1 patient each. Sinoatrial node dysfunction occurred in 1 patient after aortic arch and VSD repair.

From the total of 20 arrhythmia episodes, 15 patients required temporary intervention, 10 in the control group and 5 in the DEX group (Table 4). In the 3 patients with VTAC and no intervention, the first had an episode of 18-beat VTAC, the second had several 10- to 20-beat VTAC episodes within a 45-minute period, and the last had an episode of 15-beat VTAC. The patient with atrial bigeminy had sustained bigeminy that lasted for 65 minutes. In the DEX group, two episodes of reentrant SVT developed in 1 patient after the Norwood I procedure while receiving a dexmedetomidine infusion at 0.75 μg/kg/h. For the first episode, he received a 1-μg/kg dexmedetomidine load with immediate cardioversion to NSR, whereas for the second episode, he received adenosine with cardioversion to NSR was also successful. Of note, however, that whereas no significant hemodynamic changes were observed during the dexmedetomidine load, significant bradycardia (HR, 55 beats/min) and hypotension (mean blood pressure, 29 mm Hg) developed that lasting approximately 1 minute after the administration of adenosine. Both episodes of JET occurred in patients with an Aristotle level of 2.

Table 3. Patients With Arrhythmias and Arrhythmia Episodes

Variable	Control	DEX	*p* Value
Tachyarrhythmias, No. (%)	10 (50)	2 (6)	0.001*
Episodes, No.			
Ventricular tachycardia	6	...	
Atrial ectopic tachycardia	3	...	
Junctional ectopic tachycardia	2	...	
Reentrant SVT	1	2	
Atrial bigeminy	1	...	
Junctional accelerated rhythm	...	1	
Bradyarrhythmias, No. (%)	2 (10)	2 (6)	0.85
Episodes, No.			
Complete AV block	1	2	
Sinoatrial node dysfunction	1	...	

* Statistically significant.

AV = atrioventricular; DEX = dexmedetomidine; SVT = supraventricular tachycardia.

The HR was significantly lower in the DEX group during postoperative day 0 (Table 5). Clinically significant bradycardia requiring atrial pacing was only noted in 1 patient from each group ($p = 0.69$); however, significantly more episodes of sinus tachycardia were noted in the control group ($p = 0.008$).

Table 6 reports the remaining postoperative variables. Use of inotropic support with epinephrine and milrinone was similar in both groups, and the use or dose of epinephrine was not associated with occurrence of tachyarrhythmias ($p = 0.51$ and $p = 0.72$, respectively). Patients in the DEX group required significantly lower antihypertensive doses of sodium nitroprusside and nicardipine.

Table 5. Hemodynamic Data

Variable*	Control (n = 20)	DEX (n = 32)	*p* Value
Heart rate, beats/min			
POD 0	144 ± 5	130 ± 4	0.03†
POD 1	144 ± 5	132 ± 5	0.07
POD 2	136 ± 5	136 ± 4	0.89
SBP, mm Hg			
POD 0	87 ± 5	84 ± 4	0.61
POD 1	86 ± 4	81 ± 4	0.20
POD 2	96 ± 4	90 ± 4	0.22
Respiratory rate, breaths/min			
POD 0	49 ± 5	45 ± 3	0.36
POD 1	38 ± 4	33 ± 3	0.20
POD 2	43 ± 5	37 ± 4	0.17
Tachycardia	8 (40)	2 (6)	0.008†
Bradycardia	1 (5)	1 (3)	0.69
Hypertension	11 (55)	13 (40)	0.46
Hypotension	2 (10)	9 (28)	0.22

* Data are presented as mean ± standard error, and episodes (%) throughout the study period. † Statistically significant.

DEX = dexmedetomidine; POD = postoperative day; SBP = systolic blood pressure.

The overall sedative and analgesic requirement was similar, except the DEX group required significantly less fentanyl. One death occurred in the DEX group. This patient was never separated from CPB after the Norwood I procedure due to decreased ventricular function. A significant intracranial hemorrhage developed, and life support was withdrawn.

Table 4. Arrhythmias and Interventions

Arrhythmia	No.	Control Intervention	No.	DEX Intervention	No.
Tachyarrhythmias					
VTAC	6	None	3	...	...
		Defibrillation, lidocaine, amiodarone	1	...	...
		Defibrillation	1	...	...
		Amiodarone	1	...	...
AET	3	None	1	...	...
		Amiodarone	1	...	...
		Amiodarone, DEX	1	...	...
JET	2	Sedation, Atrial pacing	1	...	...
		Amiodarone, DEX	1	...	...
Reentrant SVT	3	Adenosine	1	DEX	1
		Adenosine	1	...	...
Atrial bigeminy	1	None	1	...	...
JAR	1	...	...	Atrial pacing × 2 hrs	1
Bradyarrhythmias					
Complete AV block	3	AV pacing × 34 hrs	1	AV pacing < 14 hrs	2
SA node dysfunction	1	Atrial pacing × 8 hrs	1	...	...

AET = atrial ectopic tachycardia; AV = atrioventricular; DEX = dexmedetomidine; JAR = junctional accelerated rhythm; JET = junctional ectopic tachycardia; SA = sinoatrial; SVT = supraventricular tachycardia; VTAC = ventricular tachycardia.

Table 6. Cardiorespiratory and Sedation and Analgesic Requirements During the Postoperative Period

Variable*	Control (n = 20)	DEX (n = 32)	*p* Value
Intubated	13 (68)	20 (62)	0.49
Duration of intubation, days	3.5 ± 0.6	3.0 ± 0.8	0.5
Mortality	0	1 (3)	0.8
Inotropic/vasotropic support			
Epinephrine, μg/kg	0.56 ± 0.16	0.86 ± 0.25	0.38
Patients taking epinephrine	10 (53)	14 (44)	0.63
Milrinone, μg/kg	49 ± 5	37 ± 4	0.06
Patients taking milrinone	20 (100)	32 (100)	NA
Nitroprusside, μg/kg	20 ± 7	4 ± 1	0.004[b]
Patients taking nitroprusside	11 (58)	9 (28)	0.07
Nicardipine, μg/kg	13 ± 5	2 ± 1	0.02[b]
Patients taking nicardipine	6 (32)	9 (28)	0.9
Sedatives/analgesics			
Dexmedetomidine, μg/kg/h		0.76 ± 0.04	
Dexmedetomidine duration, hrs		38 ± 4	
Fentanyl, μg/kg	39 ± 8	19 ± 3	0.005[b]
Patients taking fentanyl	16 (84)	18 (56)	0.08
Morphine, mg/kg	0.03 ± 0.01	0.02 ± 0.01	0.7
Midazolam, mg/kg	0.09 ± 0.02	0.07 ± 0.02	0.55
Lorazepam, mg/kg	0.02 ± 0.01	0.02 ± 0.01	0.7
Chloral hydrate, mg/kg	25 ± 6	16 ± 4	0.23

* Continuous data are shown as mean ± standard error; categoric data as number (%). [b] Statistically significant.

DEX = dexmedetomidine; NA = not applicable.

Laboratory results are summarized in Table 7. No significant difference was observed between the groups in levels of creatinine, lactates, electrolytes, or blood gases.

Comment

Despite recent advancements in pediatric cardiac critical care, ventricular and supraventricular arrhythmias can present a challenging problem when encountered in the immediate postoperative period. The combination of an excessively fast HR and the loss of atrioventricular syn-

Table 7. Laboratory Results During the Postoperative Period

Variable*	Control (n = 20)	DEX (n = 32)	*p* Value
Creatinine, mg/dL	0.41 ± 0.04	0.47 ± 0.04	0.42
Lactate, mmol/L	2.2 ± 0.2	2.6 ± 0.3	0.98
pH	7.45 ± 0.01	7.44 ± 0.01	0.66
Pco_2, mmHg	43 ± 1	42 ± 1	0.41
Po_2, mmHg	98 ± 11	124 ± 12	0.11
Hemoglobin, g/dL	14 ± 4	14 ± 3	0.84
Potassium, mmol/L	3.8 ± 0.5	3.9 ± 0.6	0.48
Magnesium, mg/dL	2.6 ± 0.4	2.7 ± 0.4	0.87
Ionized calcium, mmol/L	1.4 ± 0.2	1.3 ± 0.1	0.09

* Data are shown as mean ± standard error.

DEX = dexmedetomidine; Pco_2 = partial pressure of carbon dioxide; Po_2 = partial pressure of oxygen.

chrony are often poorly tolerated. Current standard therapies, such as electrical cardioversion, defibrillation, overdrive pacing, and intravenous antiarrhythmic agents, may be undesirable, unavailable in a timely manner, ineffective, or associated with significant adverse effects.

The efficacy of pharmacologic treatment for the prevention of postoperative arrhythmias has been the focus of investigation in a number of studies [3–6]. Pediatric studies are scarce, and as with some adult studies, have had equivocal results. In the current study, our pivotal finding was that perioperative use of dexmedetomidine decreased the incidence of ventricular and supraventricular tachyarrhythmias without significant adverse effects.

Dexmedetomidine is an α-2 adrenergic receptor and imidazoline receptor agonist with primarily sedative and analgesic properties. Since its approval by the U.S. Food and Drug Administration for use in intensive care unit adult patients more than 10 years ago, it has been increasingly used in many off-label indications, including procedural and pediatric sedation, as an anesthetic adjunct, and for opioid withdrawal [13–15]. In a recent case series study, we also demonstrated that dexmedetomidine can be used as an antiarrhythmic agent for SVTs [7]. Dexmedetomidine was used as a primary treatment in 9 patients and as a rescue treatment in 5. The primary outcome with overall rhythm or HR control was achieved in 93% of the patients. All patients with JET had conversion to NSR or HR control; all patients with reentrant SVT had resolution of their tachyarrhythmia, 1 patient

with AET had an initial HR control and then NSR within 85 minutes, 1 patient with atrial flutter failed to respond, and 2 patients with junctional accelerated rhythm had HR control.

Further substantiation of the antiarrhythmic properties of dexmedetomidine was elucidated in a carefully designed animal study by Kamibayashi and colleagues [16]. They suggested that the antiarrhythmic effects are mediated through enhancement of the vagal neural activity. The dorsal motor nucleus of vagus is an important region, where an efferent parasympathetic nerve originates, and the activity of this region is directly regulated by nucleus tractus solitarius, where an afferent vagal sensory input terminates [17]. These nuclei are both rich in α-2 receptors, and thus, it seems likely that activation of these receptors by dexmedetomidine would lead to a potent enhancement of vagal activity [18]. In their study, dexmedetomidine significantly increased the arrhythmogenic threshold of epinephrine-induced ventricular arrhythmia, an effect that was abolished in vagotomized animals.

Although this mechanism is unlikely to explain the antiarrhythmic process for all of the arrhythmias in our current study, many reports have demonstrated that enhanced vagal activity is protective against certain types of supraventricular and ventricular arrhythmias [19–21]. Similar to β-blockade, enhanced vagal output through a mechanism that involves decreased cyclic-adenosine monophosphate production, prolongs the effective refractory period of myocardial cells and decreases automaticity. Another possible mechanism involves activation of imidazoline receptors. Dexmedetomidine contains an imidazole ring and has an affinity for these receptors. Recent studies have shown that activation of central imidazoline type I receptors has been implicated in the prevention of ventricular arrhythmias [9, 22].

Given the results of our previous study, the current findings of a decreased incidence of JET, reentrant SVT, and AET, although quite significant, were not unexpected. We were surprised, however, to observe such a difference in the incidence of VTAC. These findings seem to correspond with the mentioned animal studies, all of which showed that dexmedetomidine decreased the incidence or increased the threshold, or both, for VTAC.

Despite the central α-2 adrenoreceptor–mediated sympatholysis of dexmedetomidine, we did not find a difference in the dose requirement of perioperative epinephrine or in the number of hypotensive or bradycardic episodes. On the contrary, the DEX group required fewer antihypertensive agents. We speculate that dexmedetomidine attenuates the hyper-catecholaminergic state seen after CPB, resulting in less inappropriate tachycardia and less hypertension.

Limitations with the current study include the inherent nature of a nonrandomized single-institution methodology that could not establish direct causal relationships with certainty. Some arrhythmias, such as atrial flutter and atrial fibrillation, were not detected during the study, and thus, conclusions cannot be drawn for these arrhythmias. Our observation period was only 72 hours, and we may have missed arrhythmias that occurred afterwards. Supplemental data for variables such as ventricular function were not available.

In conclusion, our findings suggest that the use of dexmedetomidine during the perioperative period for congenital cardiac operations may reduce the incidence of ventricular and SVTs without significant adverse effects. The current results are of paramount importance that can be used to perform larger randomized, double-blind trials, and therefore establish potential newer therapeutic protocols.

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DISCUSSION

DR STEPHANIE FULLER (Philadelphia, PA): Dr Morell, for your use of dexmedetomidine (DEX), we certainly had to terminate it on some of our patients who have experienced bradyarrhythmias. Can you comment on whether DEX was terminated early in any of the patients because of any bradyarrhythmias? And then secondly, did you see any new arrhythmias? You can't hear me? Sorry.

I was asking basically about terminating the use of DEX because of bradyarrhythmias. We have seen quite a few bradyarrhythmias and have had to stop our infusion of DEX. Usually, it comes back within a relatively short period of time to a normal rhythm.

And then the question of whether any of these patients had a new supraventricular tachycardia (SVT) once the DEX was terminated, for example, 12 to 24 hours later? As you know, it is an infusion that can be only used for a limited period of time.

DR MORELL: Those are very good questions. I am not aware, and I honestly don't know 100%, but the incidence of bradyarrhythmias was equally the same in both groups. And I am not aware that the arrhythmias provoked stopping the DEX drip in those 2 patients, because only 2 patients had bradyarrhythmias. And as far as I know, there were no other incidents of arrhythmias in any of those patients post-op. I mean, it is a small group of patients. We are not representing a big group of patients. But those were the incidents of arrhythmias in that group of patients during the hospitalization, what we showed.

DR HITENDU H. DAVE (Zurich, Switzerland): Based on your results, what is your recommendation for treatment of early postoperative atrial tachyarrhythmias? Would you use DEX as a first-line therapy before starting amiodarone, or do you use it as an adjunct?

DR MORELL: You know, I honestly, first of all, I don't take care of those problems. I think a lot of us, we are usually, hopefully, asleep, and the intensivist is dealing with these issues.

But, in all honesty, there are times that I come in and they tell me, well, the patient became unstable and we gave them DEX. And unfortunately, in our unit, DEX has become the drug of choice, which I don't necessarily agree with. I think if you have somebody who has had some hemodynamic compromise, in my eyes, give him amiodarone, as opposed to give him DEX. But, unfortunately, I am not being consulted for the management of those arrhythmias, so it has become, you know, we have a DEX type of unit in which everybody for any reason essentially gets DEX.

DR DAVE: But for you it is a first-line therapy. And do you see a reduction in the use of amiodarone in your practice?

DR MORELL: I really haven't looked at it specifically. But based on the result that they got, I would say yes, we use it less.

DR PETER MANNING (Cincinnati, OH): Most of these tachyarrhythmias are in some way catecholamine related. They are excitable rhythms. I am struck by the frequency that you are seeing these. It seems like it is a lot higher than what we see—we haven't looked at our numbers, so I don't know that that is a fact.

I was also struck by the fact that even though it is a pretty diverse population, with a reasonable percentage of kids undergoing early extubation, your average epinephrine infusion was something in the order of 0.06 to 0.07 in both groups, which is a lot of catecholamines for a simple ventricular septal defect (VSD). So I am wondering if what you are doing is treating an iatrogenic problem, creating a high risk of arrhythmias because of a partially iatrogenic high catecholamine milieu. There are other ways to blunt the catecholamine effect. What is your routine in terms of narcotics? Because, obviously, these kids are also getting, to some extent, analgesic for the surgical pain.

DR MORELL: Well, believe it or not, the majority of them might get intermittent morphine, but in general they are getting DEX. DEX is pretty much the drug that is utilized in our unit for the management of pain. It is an analgesic and a sedative.

VSDs don't come out, obviously, but you just saw a bunch of Norwoods. I was surprised. When I looked at that obviously, I didn't—this was an intensive care unit–driven study—when I looked at the results, I said, "Wow, look at all these kids." Especially I was also surprised at the incidence of ventricular arrhythmias as described even in Norwoods and stuff like that. But the data are the data. And that is what they found and that is what they brought out. So in my practice, I never thought it was that prevalent, and I am not sure it is truly that prevalent, it just happens in that group of patients that is what they found and that is how they manage it.

DR MANNING: So you said in the DEX group you are using that as your primary analgesic, so that the narcotic dosing was different in the two groups?

DR MORELL: Correct. And we showed that, yes.

Objetivo:

Analizar si la utilización de dexmedetomidina de forma rutinaria en el perioperatorio de cirugía cardiaca pediátrica disminuye la incidencia de taquicardia supraventricular y ventricular.

Diseño:

Estudio prospectivo de cohortes comparando 32 pacientes pediátricos que recibieron dexmedetomidina con 20 pacientes control que no recibieron dexmedetomidina.

Periodo:

Oct 2009- Junio 2010.

Población:

pacientes pediátricos intervenidos de cirugía cardiaca con circulación extracorpórea.

Variable principal:

Incidencia de taquiarritmia supraventricular y ventricular en el postoperatorio.

Variables secundarias:

duración de ventilación mecánica, soporte vasoactivo yeinotrópico y mortalidad perioperatoria.

Resultados:

Dexmedetomidina se inició después de la inducción anestésica y se mantuvo durante la cirugía y el postoperatorio durante 38 ± 4 horas (dosis media de 0,76 mcg/kg/h). Diez pacientes del grupo control y 2 del grupo dexmedetomidina desarrollaron un total de 16 episodios de taquiarritmia (p=0,001) representando una incidencia de 25% vs 0% (p=0,01) en taquicardia ventricular y 25% vs. 6% (p=0,05) en taquicardia supraventricular comparando el grupo control con el grupo que recibió dexmedetomidina. Dos pacientes en el grupo control y uno en el grupo

dexmedetomidina presentaron bloqueo AV completo. Los pacientes en el grupo control presentaron una frecuencia cardiaca superior (141 ± 5 vs. 127 ± 3 lpm, p=0,03), requirieron más medicación antihipertensiva con nitroprussiato (20 ± 7 vs. 4 ± 1 mcg/kg, p=0,004) y nicardipino (13 ± 5 vs. 2 ± 1 mcg/kg; p=0,02) y requirieron más fentanilo (39 ± 8 vs. 19 ±3 mcg/kg; p=0,005). No se detectaron diferencias significativas en cuanto a duración de la ventilación mecánica (3,5 ± 0,6 vs. 3,0 ± 0,8 días; p=0,49) y mortalidad (0 vs. 1 (3%), p=0,5) entre el grupo control y el grupo dexmedetomidina respectivamente.

Conclusión:

La utilización de dexmedetomidina en el perioperatorio de cirugía cardiaca pediátrica se asocia con una disminución significativa de la taquiarritmia.

4. **DISCUSION**

4.1. Eficacia y seguridad de dexmedetomidina en el postoperatorio de cirugía cardíaca pediátrica.

Dexmedetomidina es un sedoanalgésico con un perfil hemodinámico que lo hace atractivo para la cirugía cardiaca. A través de la estimulación de los receptores imidazólicos del *locus coeruleus* provoca un nivel de sedoanalgesia adecuado sin deprimir el centro respiratorio, lo que permite avanzar en el destete respiratorio del paciente de forma precoz y disminuir así los tiempos de ventilación mecánica y como consecuencia, la estancia media en unidades de cuidados intensivos(8-10). La eficacia y seguridad de la dexmedetomidina en el manejo de la sedoanalgesia en el perioperatorio de la cirugía cardiaca pediátrica ha sido ampliamente estudiada(11). En mi previo centro de trabajo, la unidad de cuidados intensivos cardiacos pediátricos del *Children's Hospital of Pittsburgh*, Pittsburgh (Pensilvania, USA) la utilización de Dexmedetomidina se inicio en 2004. En 2008, Chrysostomou y colaboradores, publicaron los primeros resultados de la utilización de dexmedetomidina en pacientes pediátricos de mayor edad sometidos a cirugía cardíaca de baja complejidad (35). En esta revisión retrospectiva, se evaluaron 38 pacientes con una edad media de 8 años. Treinta y tres (87%) de estos fueron extubados durante la infusión de dexmedetomidina o permanecieron en respiración espontánea. La infusión de dexmedetomidina fue bien tolerada y, en el 93 % de los pacientes se alcanzó un nivel de sedación óptimo y en un 83% de los casos se objetivó un buen control del dolor a las dosis utilizadas (dosis inicial media de 0,32±0,15 mcg/kg/h y dosis de mantenimiento de 0,31±0,05 mcg/kg/h). En esta primera publicación ya

se objetivó una tendencia a la necesidad de dosis más elevadas en los pacientes de menos de 1 año de edad (0,4±0,26 vs. 0,29±0,17 mcg/kg/h) así como la necesidad de más dosis de rescate de otros sedantes y analgésicos. A raíz de estos primeros resultados y refrendados por múltiples estudios que respaldaban nuestros hallazgos, el uso de dexmedetomidina se extendió, de forma progresiva, a pacientes de más corta edad y con patologías cardíacas más complejas. Nuestro estudio (ARTICULO 1) fue el primero en demostrar la eficacia y seguridad de la utilización de la dexmedetomidina en pacientes de pediátricos de corta edad (< 1 año) y neonatos en el postoperatorio de cirugía cardiaca. Nuestros resultados nos confirmaron que dexmedetomidina era un fármaco seguro en la población de pacientes lactantes y neonatales y que, para alcanzar los mismos efectos terapéuticos estos requerían dosis de fármaco más elevadas. Estos resultados permitieron continuar con el uso de dexmedetomidina en la unidad y permitieron ganar experiencia en el manejo del fármaco en la población de pacientes en el postoperatorio.

4.2. Dexmedetomidina y su efecto en el control de la arritmia

El estudio de los mecanismos de acción del fármaco, la experiencia acumulada y, porque no decirlo, la casualidad, hizo que observáramos efectos beneficiosos en el manejo de las taquiarritmias. La primera observación que motivó el estudio de las propiedades antiarrítmicas de dexmedetomidina fue la conversión a ritmo sinusal de una taquiarritmia por reentrada auricular en un paciente pediátrico de 12 años al que se había administrado dexmedetomidina como fármaco sedoanalgésico en preparación para la cardioversión eléctrica. Estas observaciones motivaron la utilización de dexmedetomidina en

pacientes que presentaban episodios de taquiarritmia supraventricular por reentrada. Los resultados de esta experiencia se derivaron en dos publicaciones: 1) el artículo 2, que valora la utilidad de dexmedetomidina en el control de la taquicardia paroxística supraventricular y 2) un estudio retrospectivo en el que se analizaba la utilización de dexmedetomidina en 12 pacientes en los que se había administrado para controlar la taquiarritmia postoperatoria. Los resultados de estas dos publicaciones y, en particular los del ARTÍCULO 2, son de gran importancia porque sugieren un posible papel antiarritmogénico de la dexmedetomidina más allá del directamente derivado del bloqueo de la respuesta catecolaminérgica. El mecanismo exacto de la cardioversión farmacológica provocada por dexmedetomidina no está todavía bien dilucidado. A falta de estudios electrofisiológicos orientados a estudiar este mecanismo lo que sabemos, en base a nuestra experiencia, y que resulta la base de nuestra hipótesis de trabajo, es que la activación del sistema nervioso autonómico juega un papel relevante tanto en el origen como mantenimiento de las arritmias en general y de la taquiarritmia por reentrada en particular. Además, sabemos que el tejido del nodo AV tiene una abundante inervación autonómica con fibras parasimpáticas vagales y fibras simpáticas torácico espinales. Por ello, dexmedetomidina, un agonista α-2 con propiedades simpaticolíticas y parasimpaticomiméticas lo convierte en un agente ideal para la taquiarritmia por reentrada en la que se ve afectado el nodo AV. El núcleo motor dorsal del nervio vago da origen a fibras eferentes parasimpáticas. La actividad de esta región está directamente regulada por el núcleo del tracto solitario lugar en el que termina un estimulo sensorial aferente vagal. Ambos núcleos disponen de abundantes

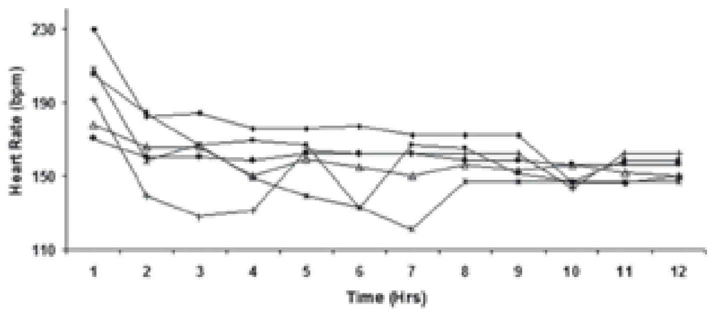
receptores α-2 adrenérgicos y su activación, por dexmedetomidina, podría conducir a una potente estimulación de la actividad vagal que generaría un enlentecimiento suficiente de la conducción del nodo AV para terminar la taquiarritmia. Un estudio electrofisiológico realizado por Hammer y colaboradores objetivó disminución de la función de la conducción del nodo AV (incremento de la longitud de ciclo de bloqueo nodal) como consecuencia de la administración de una dosis de carga de dexmedetomidina. Así mismo, en nuestro estudio (ARTICULO 2) hay datos que sugieren que dexmedetomidina interfiere en la conducción del nodo AV. En varios de los casos en los que en el registro electrocardiográfico se identifica la onda p, la taquiarritmia finaliza con una p retrógrada. Esto sugiere un bloqueo anterógrado de la conducción por el circuito de reentrada a nivel del nodo AV y una persistencia de la conducción retrógrada por la vía accesoria.

Como he comentado anteriormente, nuestra experiencia inicial en la utilización de Dexmedetomidina para el control de la arritmia en el posotoperatorio inmediato fue publicada por Chrysostomou en 2008(36). En este estudio observamos como dexmedetomidina resultaba eficaz en convertir a ritmo sinusal arritmias supraventriculares por reentrada y ejercía un control eficaz de la frecuencia cardiaca en taquirritmias automáticas como la JET, permitiendo un rescatar de forma adecuada la sincronía AV con el marcapasos secuencial. En concreto, dexmedetomidina se usó como tratamiento primario en nueve pacientes y como tratamiento de rescate en otros cinco pacientes (Figura 6).

	Age (D)	Weight (Kg)	Cardiac diagnosis	Operation	Arrhythmia	Treatment
1	6	3.2	d-TGA	C	JET	Rescue
2	38	3.5	SV-TAPVRO	PVR	JET	Primary
3	7	3.5	TA II	C	JET	Primary
4	23	2.4	TOF/PAT	C	JET	Primary
5	6 mo	6	AVSD	C	JET	Primary
6	6	3.2	HLHS	Norwood I	JET	Primary
7	8	3	HLHS	Preop	Re-SVT	Primary
8	43	3.7	CHF	None	Re-SVT	Rescue
9	4	3	d-TGA	C	Re-SVT	Primary
10	1	2.8	HLHS-PAPVRO	PVR	Re-SVT	Rescue
11	4 mo	4	DORV-PS	C	JAR	Primary
12	3 mo	5.8	AVSD	C	JAR	Primary
13	12 mo	8	TA II	C*	AF	Rescue
14	5	3.9	d-TGA	C	AET	Rescue

AET = atrial ectopic tachycardia; AVI = aortic valve insufficiency; AVR = aortic valve replacement; AVSD = atrioventricular septal defect; CHF = congestive heart failure; C = complete repair; d-TGA = transposition of the great arteries; DORV-PS = double outlet right ventricle with pulmonic stenosis; HLHS = hypoplastic left heart syndrome; JAR = junctional accelerated rhythm; JET = junctional ectopic tachycardia; MVI = mitral valve insufficiency; MVR = mitral valve replacement; PVR = pulmonary vein repair; Re-SVT = reentry type supraventricular tachycardia; SV-TAPVRO = single ventricle with obstructed total anomalous pulmonary venous return; TA II = truncus arteriosus type II; TOF/PAT = tetralogy of fallot/pulmonary atresia; VSD = ventricular septal defect.

* Complete repair 3 mo prior.



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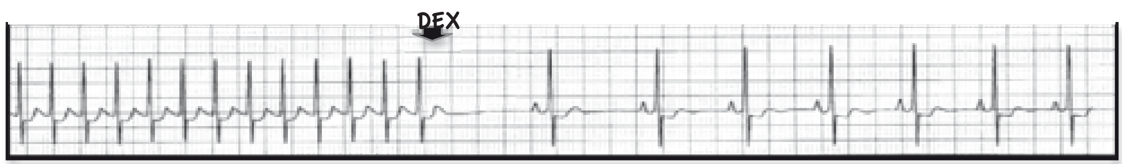
◎◎ ◎; p2 ; ap ◎ e ioi2p◎ i1o; ◎p ro; ◎sar 2; ◎ ◎sv◎os2s2; ◎p
◎ó e ◎ p se i◎ioh ;



ro; g◎ io p ◎so; pn ri◎◎ ◎ip p -i◎ra◎ ; ◎ p1gi◎◎; g-2 ◎ p1; ro; ◎sop-sa;
◎ ◎ r◎ s; ◎p ap -◎ r◎ ◎ip p -i◎ra◎ ;q; ro p gs2p-is-; ◎sov◎ 2i1o; -ipe s;
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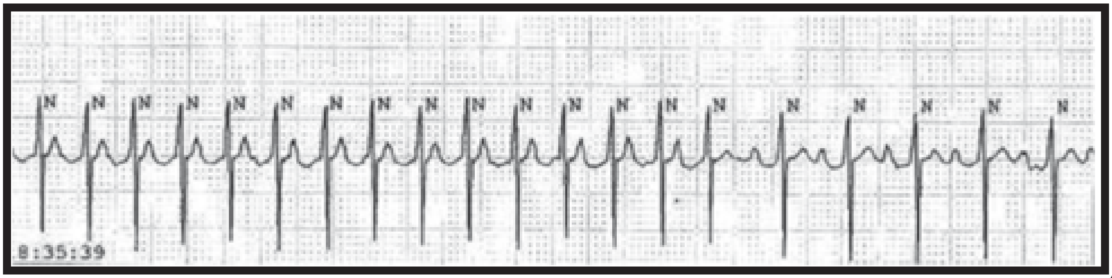

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◎◎ ◎ ◎ ó g◎ i◎ ◎i◎ g-◎ ie io◎ ; ◎◎ iv1; ◎ ; ◎ pr ◎is; gs2p◎ is-; 9◎ ◎◎◎◎ ◎ ◎◎ z◎ ◎ ◎◎◎ SR◎ ;◎ ;nr ◎ ◎ pr ◎ie s2; ◎◎ s-e ◎ g-s2g◎ piv◎ ◎ ; ie g◎ ps; ◎◎ a◎ r piaiu◎ i1o; ◎◎ ◎ó e ◎ p se i◎io◎ ◎◎2◎◎ a◎ io◎r ◎◎i1o; ◎ ◎ pá2i◎◎ q;◎r -◎ p◎ ◎ ;gs2ps g◎ p s-is;ioe ◎ ip s;◎ ;a◎ g-v◎ ◎ ◎i1o;◎◎ a◎ p◎ r i◎ -ipe i◎ gs2ps g◎ ◎ps-i◎h ; ◎◎ ◎D2nr ◎ ◎ ◎◎ r o; p-p◎ i◎ ps; ◎ e ◎ sa1Ui◎s; ◎ ; a◎ g-v◎ ◎ ◎i1o; ◎◎; a◎ p◎nr i◎ -ipe i◎ g◎ is g◎ p s-i◎; t ◎ 2i◎s;◎ ; s◎s;◎◎;p ◎ ◎i1o;◎◎ e Dapiga◎ ;p-◎ b s2;◎◎ iov◎ piU◎ i1oh;◎ ;◎B◎ ◎◎ t sq;g◎ ◎ ◎ nr ◎ a◎ r piaiu◎ i1o;◎◎ e ◎U o◎ is;◎◎ s-e ◎ g-s iampi◎◎ ◎ ;a◎ ; 2sar ◎iso◎ ; ◎◎ g◎ r 2i1o; ◎ ; ◎ ; ◎i-◎r ips; ◎◎ ◎i-◎r a◎ i1o; ó p-◎ s-g1-◎ ◎r -◎ p◎; a◎ ◎i-r UB◎ ◎ ; a◎ Doi◎◎ iop◎ vo◎ ◎i1o; nr ◎ -◎ r ap◎ ◎ i◎u; ◎ ; a◎ g-v◎ ◎ ◎i1o;◎◎ a◎ p◎ r i◎ -ipe i◎ gs2ps g◎ p s-i◎; 9HAhR◎o;◎ p◎ 2◎ pi◎s5;◎ ; g-sgi◎ ◎ ◎ ;◎ pi◎p◎ ◎ sa◎ ioá-Ui◎◎ ; ◎◎ ◎ó e ◎ p se i◎io◎ os2; t i◎i◎ so; ga◎ p◎ ; 2r ; gs2i◎a◎ gg ◎ ; ◎ ; a◎ g-v◎ ◎ ◎i1o; q; ◎sop-sa; ◎◎ ◎ r ◎ a◎ ; ◎ -ipe i◎ ; gs2ps g◎ p s-is2; ◎se s; a◎ ◎◎◎5;◎ ; a◎ ; nr ◎ g◎ ◎ ◎ nr ◎ ◎ ; psos; ◎ -◎ á-Ui◎s; p◎ ; q; ◎se s; g-◎ ◎ p◎ s2; ◎ ; a◎ iop-s◎r ◎◎i1o5 pi◎ ◎ r o;

importante factor desencadenante. A través de la estimulación de los receptores del sistema simpático periférico α-2, dexmedetomidina disminuye la liberación de catecolaminas endógenas. Existen referencias aisladas en la literatura científica del efecto antiarrítmico de dexmedetomidina. Hayashi y colaboradores en 1999, en un estudio experimental con perros, objetivaron que la infusión continua de dexmedetomidina aumentaba 4 veces el umbral arritmogénico de la adrenalina en los animales anestesiados con halotane(12). Los resultados espectaculares de este estudio pasaron desapercibidos, de forma sorprendente, en la comunidad asistencial durante las dos últimas décadas. Nuestro estudio (ARTICULO-ANEXO 1) presenta la primera evidencia científica clínica de que la utilización de dexmedetomidina durante el perioperatorio de cirugía cardíaca disminuye de forma significativa la incidencia de taquiarritmia postoperatoria.

Además, este bloqueo de la respuesta catecolaminérgica, puede ofrecer ventajas en otras esferas del desarrollo del paciente pediátrico sometido a cirugía cardiaca. Estudios experimentales sugieren un posible papel neuroprotector de la dexmedetomidina en determinados estados de hiperestimulación adrenérgica secundarios a hipoxia-isquemia cerebral como pueden ser el traumatismo craneoencefálico severo o, en el caso que nos ocupa, la cirugía cardíaca pediátrica (15,16). Así pues, estos resultados aportan la primera evidencia clínica de la utilidad de dexmedetomidina tanto en el tratamiento como en el manejo de la taquiarritmia. A partir de aquí, es necesario llevar a cabo ensayos clínicos randomizados con una potencia más elevada que confirmen la utilidad de dexmedetomidina en el control de la arritmia postoperatoria.

5. CONCLUSIONES

1) Dexmedetomidina es un fármaco seguro en la población neonatal y pediátrica de menos de 1 año de edad.

2) Dexmedetomidina és un fármaco útil en el tratamiento de la taquicardia paroxística supraventricular a través de un efecto directo a nivel de la conducción del nodo AV

3) Las propiedades simpaticolíticas hacen que dexmedetomidina controle de forma efectiva taquiarritmias postoperatorias que dependen de la excesiva descarga catecolaminérgica derivada de la respuesta sistémica al estrés quirúrgico y a la utilización de fármacos inotrópicos con actividad adrenérgica.

4) Las propiedades sedoanalgésicas de dexmedetomidina junto al doble efecto antiarrítmico de dexmedetomidina la convierten en el fármaco ideal para el control de la sedación y analgesia del postoperatorio cardiaco y la prevención de la taquiarritmia postoperatoria.

6. FUTURAS DIRECCIONES.

Creemos que es nuestra obligación continuar esta línea de investigación puesto que la confirmación de estos resultados permitiría abrir nuevos horizontes en el manejo del postoperatorio de cirugía cardiaca pediátrica en particular pero también de la cirugía cardíaca adulta, reduciendo así de forma significativa la morbilidad y mortalidad de una de las complicaciones más frecuentes que acontece en el postoperatorio de estos pacientes.
Por todo ello, en estos momentos estamos pendientes de iniciar dos ensayos clínicos derivados de los resultados de estos datos preliminares.

1) Ensayo clínico aleatorizado a doble ciego comparando dexmedetomidina versus placebo en la prevención de la taquiarritmia en el postoperatorio de cirugía cardiaca pediátrica.

2) Ensayo clínico multicéntrico aleatorizado comparando dexmedetomidina versus adenosina en el tratamiento de la taquicardia paroxística supraventricular.

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8.1. ANEXO 2 (ARTÍCULO 4)

Date: 28/01/2013
To: "Joan Sanchez-de-Toledo" joansdt@gmail.com
From: "Rev Esp Cardiol" rec@revespcardiol.org
Subject: Decisión artículo / Article decission
Ms. Ref. No.: REC-D-13-00011

TITULO: Prevención del síndrome de abstinencia en el postoperatorio de trasplante cardíaco pediátrico: Utilidad de la Dexmedetomidina. Dexmedetomidine for the prevention of opioid withdrawal syndrome after pediatric heart transplantation.

Estimado Dr. Sanchez-de-Toledo,

Tengo el placer de comunicarle que su artículo de ref. REC-D-13-00011 ha sido aceptado para publicación en nuestra Revista.

Muchas gracias por enviar su trabajo a Revista Española de Cardiología.

Reciba un cordial saludo,

Magda Heras
Editora Jefe

a. Primera pagina / First page

Prevención del síndrome de abstinencia en el postoperatorio de trasplante cardíaco: utilidad de la Dexmedetomidina

Dexmedetomidine for Prevention of Opioid Withdrawal Syndrome After Pediatric Heart Transplantation

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***b. Manuscrito / Manuscript**

Sra Editora,

Opiáceos y benzodiazepinas son los fármacos de elección en la sedoanalgesia en unidades de cuidados intensivos (UCIs) cardiacos pediátricos. El uso prolongado de estos fármacos se asocia al desarrollo de síndrome de abstinencia. Su diagnóstico en la edad pediátrica es complejo debido a un amplio espectro de sintomatología no específica y la escasez de escalas diagnósticas validadas. Su incidencia en pediatría se sitúa entre el 35-57%, siendo más frecuente cuanto mayor es la dosis acumulada y la duración del tratamiento[1]. Dosis de fentanilo acumuladas mayores de 1,6 mg/kg o infusiones superiores a 5 días se asocian al desarrollo de síndrome de abstinencia y, con dosis superiores a 2,5 mg/kg o infusiones de más de 9 días se han descrito incidencias de hasta el 100%[2].

En el trasplante cardiaco pediátrico, debido a la escasez de donantes, los tiempos en lista de espera se incrementan, aparece la necesidad de soporte circulatorio extracorpóreo, se prolongan las estancias en UCIs y aumenta la probabilidad de desarrollar síndrome de abstinencia[2]. Dexmedetomidina, un agonista alpha2 adrenérgico, es un agente sedoanalgésico con posible efecto beneficioso para el control del síndrome de abstinencia[3]. Su capacidad para producir sedación y analgesia sin provocar depresión del centro respiratorio, se ha traducido en una gran aceptación en las UCIs pediátricas en EEUU. Existen numerosas publicaciones acerca de su eficacia y seguridad[3]. Sin embargo, existe poca evidencia sobre su uso en la prevención del síndrome de abstinencia, particularmente en el postoperatorio de trasplante cardiaco (4).

Describimos nuestra experiencia con dexmedetomidina en el manejo del síndrome de abstinencia y como facilitador de la retirada de opiáceos en dos pacientes pediátricos trasplantados cardiacos.

Caso 1: lactante de 11 meses trasplantada por miocardiopatía dilatada por miocarditis; precisó soporte con oxigenación con membrana extracorpórea (ECMO) durante 7 días e implantación de dispositivo de asistencia ventricular (DAV) durante 20 días previo al trasplante. Recibió sedoanalgesia en infusión continua con opiáceos, benzodiacepinas y propofol. Presentó síndrome de abstinencia con imposibilidad para disminuir la dosis de morfina, a pesar de haberse iniciado manejo habitual del mismo. La dosis acumulada de opiáceos fue de 1'39mg/kg en 33 días. Se decidió iniciar tratamiento con dexmedetomidina en infusión continua a dosis inicial de 0'75 mcg/kg/hora y máxima de 1mcg/kg/hora, permitiendo el descenso de opiáceos de forma rápida sin reaparición de abstinencia (figura 1a). La paciente se mantuvo hemodinámicamente estable tras el inicio de dexmedetomidina y no se objetivaron efectos secundarios derivados de su uso (tabla 1a)

Caso 2: niño de 5 años trasplantado por miocardiopatía no compactada; ingresado previamente durante 11 meses con DAV, precisó ECMO durante 5 días en el postoperatorio. Recibió sedoanalgesia en infusión continua con opiáceos, benzodiacepinas y propofol. Presentó síndrome de abstinencia con imposibilidad para disminuir la dosis de morfina. La dosis acumulada de opiáceos fue de 1'21mg/kg en 16 días. Se decidió iniciar dexmedetomidina en infusión continua a 1mcg/Kg/hora. Tras el inicio de dexmedetomidina, se disminuyó la dosis de morfina en 6 días sin reaparición de abstinencia. En ese momento, fue diagnosticado de rechazo humoral, precisando cambio de sedoanalgesia para realizar pruebas diagnósticas y canalización de accesos venosos. Se suspendió dexmedetomidina durante 4 días, incrementando morfina y asociando propofol. Posteriormente se reinició dexmedetomidina, se suspendió propofol y se disminuyó morfina pudiéndose retirar de forma completa a los 7 días (figura 1b). El paciente se mantuvo hemodinámicamente estable y no se objetivaron efectos secundarios por dexmedetomidina (tabla 1b)

En ambos casos, la utilización de dexmedetomidina en la prevención del síndrome de abstinencia por opiáceos en el contexto del postoperatorio de trasplante cardiaco fue beneficioso, hemodinámicamente bien tolerada y no se asoció a ningún efecto adverso.

Al igual que nosotros, Finkel y colaboradores describieron el efecto beneficioso de la dexmedetomidina en el destete de opiáceos en dos pacientes pediátricos durante el postrasplante cardiaco[9]. En el corazón denervado, la farmacodinamia de los medicamentos depende del sitio de acción de los mismos. Fármacos con efecto directo en receptores del corazón donante serán efectivos, mientras que aquellos que actúen a nivel central o mediante reflejos autonómicos no tendrán la respuesta esperada[18]. En nuestros pacientes, dexmedetomidina pudo haber sido beneficiosa por dos mecanismos: en primer lugar, bloqueando la respuesta catecolaminérgica asociada al síndrome de abstinencia, reflejada por ausencia de hipertensión y taquicardia; en segundo lugar, porque la denervación cardiaca previno la bradicardia, efecto adverso central de la dexmedetomidina. En referencia a este segundo punto, la mayoría de pacientes en el postrasplante cardiaco o en el postoperatorio de cirugía cardiaca pediátrica, disponen de cables de marcapasos que permitirían aumentar la frecuencia cardiaca en caso de ser necesario. Estas observaciones confirman que dexmedetomidina es un fármaco beneficioso no solo como adyuvante a la sedación sino como prevención de la abstinencia en el postoperatorio de cirugía cardiaca y, en particular, del trasplante cardiaco. Es preciso llevar a cabo estudios prospectivos de mayor potencia que establezcan protocolos de utilización.

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