INSTITUTO DE MEDICINA INTEGRAL PROF. FERNANDO FIGUEIRA PROGRAMA DE PÓS-GRADUAÇÃO *STRICTO SENSU*

MESTRADO EM SAÚDE INTEGRAL

PRESSÃO POSITIVA CONTÍNUA NAS VIAS AÉREAS DURANTE A INDUÇÃO DE ANESTESIA PARA CIRURGIA PEDIÁTRICA: ENSAIO CLÍNICO RANDOMIZADO

JAYME MARQUES DOS SANTOS NETO

SETEMBRO/2019

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Dissertação apresentada no Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) como parte dos requisitos para obtenção do grau de Mestre em Saúde Integral

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Orientadora: Flávia Augusta de Orange Lins da Fonseca e Silva

Co-Orientadoras: Lívia Barbosa de Andrade e Rebeca Gonelli Albanez da Cunha Andrade

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Aos meus professores

À minha família; em particular, aos meus pais

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RESUMO

INTRODUÇÃO: pacientes pediátricos apresentam com mais frequência episódios de dessaturação durante a indução de anestesia geral (4-10%). Pressão Positiva Contínua na Via Aérea (CPAP) é um modo ventilatório que pode melhorar a troca gasosa alveolar nesse período, minimizando a formação de atelectasia e aumentando a capacidade residual funcional.

OBJETIVOS: determinar a efetividade do CPAP durante a indução anestésica em prolongar o tempo de apneia seguro (tempo em apneia até que a saturação da hemoglobina caia a 95%).

MÉTODOS: ensaio clínico, fase III, paralelo, randomizado desenvolvido no Hospital das Clínicas da Universidade Federal de Pernambuco com crianças divididas em grupos CPAP e Controle (34 em cada). Foram incluídas crianças em idade pré-escolar, estado físico I ou II, segundo a sociedade americana de anestesiologistas, submetidas a cirurgia eletiva sob anestesia geral. As variáveis estudadas: tempo entre o início da apneia e a queda da saturação periférica da oxihemoglobina (SpO_2) a 95% (T1), tempo para recuperação da SpO_2 a níveis pré-apneia (T2), tempo entre o início da apneia e a queda da SpO_2 a 95% apenas entre os pacientes em que houve queda da SpO_2 a 95% (T3), frequência de queda da SpO_2 a 95% e análise de sobrevida, levando em consideração o tempo até a queda da SpO_2 a 95%. Na análise estatística, foram utilizados para as variáveis categóricas os testes qui-quadrado de associação com correção de Yates e o teste exato de Fisher quando indicado. Também foi calculada a razão de risco (RR) como medida do risco relativo e o seu intervalo de confiança a 95%. Em relação às

variáveis numéricas, foram utilizadas média e desvio-padrão, além do teste t de *Student*. Para testar a normalidade da amostra, foi aplicado o teste de Shapiro-Wilk. Na análise de sobrevida, foi calculada a probabilidade acumulada para avaliar as chances que cada individuo do estudo tinha de atingir uma SpO_2 de 95% entre o início do estudo até um tempo máximo de cinco minutos, utilizando o método de Kaplan-Meier. As curvas de sobrevivência foram comparadas usando o teste de log-rank (Mantel-Cox). Foram construídas também curvas para cada grupo com as médias das SpO_2 medidas a intervalos regulares mediante o ajuste por um modelo de regressão para dados correlacionados que também avaliou a significância do tempo, grupo e a interação entre eles. As comparações de médias entre os dois grupos, em um dado tempo, foram realizadas com o teste de Wald. Foi considerado significante um $p<0,05$

RESULTADOS: T1 foi superior no grupo CPAP em comparação com o grupo Controle [227,65±84,74 segundos *vs*. 133,68±70,39 segundos, $p<0,0001$]. Não houve diferença entre os grupos quanto ao T2 [38,65±49,07 segundos *vs*. 43,12±60,64 segundos, $p=0,79$], enquanto o T3 foi estatisticamente significativo (161,17±61,91 segundos *vs*. 123,28±58,12 segundos, $p=0,038$). A análise de sobrevida mostrou que a sobrevivência foi superior no grupo CPAP em comparação com o grupo controle (teste Log Rank, $p = 0,0001$). Uma frequência maior de pacientes no grupo CPAP manteve saturação superior a 95% [17/34 (50%) *vs*. 2/34 (5,9%), RR 0,5313, IC95% 0,37-0,75, $p<0,0001$]. Os valores de saturação em medidas repetidas foram superiores no grupo CPAP.

CONCLUSÕES: CPAP durante a indução anestésica foi efetiva em prolongar o tempo de apneia seguro em crianças submetidas a anestesia geral para cirurgia eletiva.

PALAVRAS-CHAVE: pressão positiva contínua nas vias aéreas; hipóxia; anestesia geral; pediatria.

Número de registro de ensaio clínico (ClinicalTrials.gov): NCT03432390

ABSTRACT

INTRODUCTION: Pediatric patients have more frequent episodes of desaturation during general anesthesia induction (4-10%). Continuous Positive Airway Pressure (CPAP) is a ventilatory mode that can improve alveolar gas exchange during this period, minimizing the formation of atelectasis and increasing functional residual capacity.

OBJECTIVES: To determine the effectiveness of CPAP during anesthetic induction in prolonging safe apnea time (apnea time until hemoglobin saturation drops to 95%).

METHODS: Phase III, randomized, parallel clinical trial developed at the Federal University of Pernambuco's Teaching Hospital with children divided into CPAP and Control groups (34 in each). Preschool children, physical status I or II, according to the American Society of Anesthesiologists, who underwent elective surgery under general anesthesia were included. The variables studied: time between onset of apnea and decrease in peripheral oxyhemoglobin saturation (SpO2) to 95% (T1), time to recovery of SpO2 at pre-apnea levels (T2), time between onset of apnea and 95% SpO2 drop only among patients with a 95% SpO2 drop (T3), 95% SpO2 drop frequency, and survival analysis, taking into account the time to 95% SpO2 drop. For statistical analysis, the chi-square association tests with Yates correction and Fisher's exact test were used for categorical variables when indicated. The risk ratio (RR) was also calculated as a measure of relative risk and its 95% confidence interval. Regarding numerical variables, mean and standard deviation were used, in addition to Student's t-test. To test the normality of the sample, the Shapiro-Wilk test was applied. In the survival analysis, the cumulative probability was calculated to assess the odds that each study subject had to

achieve a SpO2 of 95% from baseline to a maximum of five minutes using the Kaplan-Meier method. Survival curves were compared using the log-rank test (Mantel-Cox). Curves were also constructed for each group with SpO2 averages measured at regular intervals by adjusting by a regression model for correlated data that also assessed the significance of time, group and the interaction between them. Mean comparisons between the two groups at a given time were performed with the Wald test. A $p < 0.05$ was considered significant.

RESULTS: T1 was higher in the CPAP group compared to the Control group [227.65 + 84.74 seconds vs. 133.68 + 70.39 seconds, $p < 0.0001$]. There was no difference between groups regarding T2 [38.65 + 49.07 seconds vs. 43.12 + 60.64 seconds, $p = 0.79$], while T3 was statistically significant (161.17 + 61.91 seconds vs. 123.28 + 58.12 seconds, $p = 0.038$). Survival analysis showed that survival was higher in the CPAP group compared with the control group (Log Rank test, $p = 0.0001$). A higher frequency of patients in the CPAP group maintained a saturation greater than 95% [17/34 (50%) vs. 2/34 (5.9%), RR 0.5313, 95% CI 0.37-0.75, $p < 0.0001$]. Saturation values in repeated measures were higher in the CPAP group.

CONCLUSIONS: CPAP during anesthetic induction was effective in prolonging the safe apnea time in children undergoing general anesthesia for elective surgery.

KEY WORDS: Continuous Positive Airway Pressure, Hypoxia, General Anesthesia, Pediatrics.

TRIAL REGISTRY NUMBER (ClinicalTrials.gov): NCT03432390

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LISTA DE SIGLAS, SÍMBOLOS E ABREVIATURAS

ASA	*American Society of Anesthesiologists*
CEP	Comitê de Ética em Pesquisa em Seres Humanos
cmH_2O	Centímetro de Água
CO_2	Dióxido de carbono
CPAP	Pressão Positiva Contínua na Via Aérea
CRF	Capacidade Residual Funcional
FiO_2	Fração inspirada de Oxigênio
G	Gauge
HC-UFPE	Hospital das Clínicas da Universidade Federal de Pernambuco Professor Romero Marques
g/m^2	Grama por metro quadrado
IMIP	Instituto de Medicina Integral Prof. Fernando Figueira
l/min	Litros por minuto
mg/kg	Miligramas por quilograma
O_2	Oxigênio
PaO_2	Pressão arterial de Oxigênio
$PaCO_2$	Pressão arterial de dióxido de carbono
PCR	Parada Cardiorrespiratória
PEEP	Pressão Expiratória Final na Via Aérea
TCLE	Termo de Consentimento Livre e Esclarecido
VO_2	Consumo de oxigênio
V/Q	Relação ventilação/perfusão

I. INTRODUÇÃO

Anestesia geral pode ser definida como um estágio transitório de inconsciência induzido por fármacos através de suas ações em receptores moleculares[1,2]. Pouco ainda é conhecido sobre seus mecanismos, mas supõe-se que esse estado seja um fenômeno adaptativo assim como o sono[1]. Trata-se de uma condição reversível que apresenta padrões comportamentais e fisiológicos específicos (inconsciência, amnésia, analgesia e acinesia). Consiste de três fases: indução, manutenção e emergência ou despertar[2].

A indução anestésica é o período em que há o início da administração dos fármacos hipnóticos (venosos, inalatórios ou uma combinação de ambos)[2,3]. Nessa fase, um padrão respiratório irregular progride para apneia. Assistência ventilatória é então iniciada pelo anestesiologista, normalmente através de máscara facial e bolsa reservatório[2,4].

Indução inalatória é uma técnica segura, factível e bem aceita pelos pacientes, utilizada amplamente em crianças ou, excepcionalmente, em adultos com acesso venoso difícil. Entretanto, não é um método isento de riscos. Complicações como tosse, laringoespasmo, salivação, falha de indução e apneia voluntária podem aumentar a morbidade do procedimento anestésico[3,5].

Os efeitos da anestesia geral sobre o sistema respiratório são bem estabelecidos, e, dentre eles, destaca-se a maior predisposição para obstrução e colapso da via aérea. Seus mecanismos não são claramente conhecidos apesar de algumas associações serem documentadas (relaxamento da musculatura ventilatória, relação dose-efeito do nível de anestesia e comprometimento da patência da via aérea)[6,7]. A perda do tônus da

musculatura respiratória, decorrente da indução anestésica, está relacionada a colapso das vias aéreas inferiores, reduzindo a capacidade residual funcional (CRF)[7].

Outra explicação aditiva ao colapso das vias aéreas é o impacto farmacológico das drogas utilizadas para a sedação e hipnose nos processos que controlam tanto as vias eferentes motoras da musculatura faríngea como a aferência dos mecanorreceptores[6].

Os anestésicos inalatórios exacerbam o colapso dinâmico das vias aéreas, em especial no palato mole, tendo associação direta com a dose administrada da droga. O sevoflurano atua reduzindo a atividade fásica inspiratória do músculo genioglosso sem comprometer sua atividade tônica. Mesmo em níveis sedativos, o sevoflurano modifica as dimensões das vias aéreas, reduzindo sua patência especialmente na inspiração[6].

Assim como os fármacos inalatórios, os anestésicos venosos também apresentam ação sobre o sistema respiratório. O propofol reduz a área de secção transversal da via aérea superior, redução que se mostrou máxima na base da língua quando doses sedativas são utilizadas. A indução com esse agente reduz a atividade eletromiográfica do músculo genioglosso[6].

Durante o período de apneia que se segue à indução da anestesia geral, as reservas de oxigênio (O_2) vão sendo consumidas o que pode resultar em hipoxemia[8]. A dessaturação da oxihemoglobina é mais rápida em pacientes com capacidade reduzida de transporte de O_2, ou seja, naqueles com diminuição da CRF, da pressão parcial de oxigênio (PaO_2), do conteúdo arterial de oxigênio e do débito cardíaco, ou aumento do consumo de oxigênio (VO_2)[9].

Anestesia geral aparece como fator de risco maior de mortalidade em pacientes pediátricos cirúrgicos, bem como problemas no manejo da via aérea em pacientes com

comorbidades parece adicionar risco de vida à essa população[10]. Os pacientes pediátricos, por sua vez, apresentam com mais frequência episódios de dessaturação durante a indução (4-10%)[5,8,11,12].

A imposição de dificuldades ao manejo da via aérea aumenta sobremaneira a incidência de eventos respiratórios, tais como laringoespasmo e broncoespasmo, e cardiovasculares [parada cardiorrespiratória (PCR)][13]. Crianças submetidas a um maior número de tentativas de intubação traqueal, consideradas portadoras de via aérea difícil, estão sob maior risco de dessaturação que pode evoluir naturalmente para hipoxemia[12]. A ocorrência dessa durante a manipulação das vias aéreas em crianças pode vir acompanhada de complicações ainda mais graves como PCR e morte[11].

A queda da saturação da oxihemoglobina a níveis menores que 95% induz a alterações em parâmetros hemodinâmicos como o índice sistólico, razão entre o índice cardíaco (volume sistólico x frequência cardaca/superfície corporal) e frequência cardíaca, o que sinaliza uma redução da função do coração[14].

Um estudo observacional, realizado na Índia no centro avançado de pediatria de um hospital terciário num período de cinco anos, documentou todas as paradas cardíacas ocorridas nos procedimentos cirúrgicos com administração de anestesia, fossem eletivas ou de emergência, num total de 12.158 cirurgias. A população do estudo compreendeu desde neonatos até pacientes com 18 anos de idade. Os eventos respiratórios foram responsáveis por 29% das paradas cardíacas perioperatórias em crianças. Essa participação aumenta para mais da metade (56%) quando são analisados os fatores relacionados de alguma maneira à anestesia. Todas as PCR atribuídas exclusivamente ao ato anestésico ocorreram durante a indução anestésica[15].

Em outro estudo observacional (10.649 anestesias) realizado no Brasil através de questionário com dados de um período de seis anos, foram analisadas todas as paradas cardíacas ocorridas em sala de cirurgia ou na sala de recuperação pós-anestésica de um hospital universitário. A base de dados abrangeu os procedimentos cirúrgicos realizados em crianças menores de 18 anos. Os resultados apontaram os problemas no manejo de via aérea como a maior causa de PCR relacionada à anestesia[16].

Características anatômicas próprias podem contribuir para ocorrência de hipoxemia em crianças no perioperatório, tais como: 1) cabeça e língua proporcionalmente grandes; 2) hipertrofia de adenóides e amígdalas; 3) hipofaringe menor e mais estreita; 4) laringe mais alta na altura do pescoço; 5) cordas vocais inclinadas, e não em ângulo reto; 6) epiglote em formato de "U" invertido; e 7) menor diâmetro das vias aéreas em comparação com os adultos, o que impõe mais resistência ao fluxo de ar de acordo com a lei de Poiseulle ($R = 8\eta L/\pi r^4$). Todos esses fatores implicam em desafios diários à manipulação da via aérea, seja na ventilação, seja durante a intubação[17]. Em lactentes, ocorre fechamento das vias aéreas durante a indução da anestesia geral, primariamente na direção antero-posterior, sendo uniforme em toda a faringe, o que muda em crianças mais velhas nas quais a epiglote é o ponto de maior estreitamento[6].

As características fisiológicas dos pacientes pediátricos, tais como, menor CRF, maior VO_2, maior produção de gás carbônico (CO_2) e incidência maior de complicações respiratórias durante o período de indução quando há interrupção da oferta de O_2, também contribuem para a queda na saturação de oxigênio pela hemoglobina[9,11,17,18]. A idade tem ainda correlação linear com a duração da apneia antes da dessaturação da

oxihemoglobina, assim como quanto menor o peso do paciente maior a incidência de episódios graves do evento[8,11] e os riscos de obstrução e dessaturação parecem ser maiores em crianças até três anos[6].

Uma das estratégias que podem ser usadas pelo médico anestesiologista para a manutenção adequada das reservas de oxigênio, e assim evitar complicações tais como a hipoxemia, é a pré-oxigenação. A oferta de O_2 em níveis acima dos habitualmente respirados pelo paciente tem como objetivo aumentar seus estoques e prolongar o período de tempo antes da dessaturação da oxihemoglobina[9,11,19]. Em modelos teóricos, as reservas fisiológicas corporais de O_2 (pulmão, plasma e hemoglobina) podem aumentar em mais de duas vezes e meia quando a fração inspirada daquele gás (FiO_2) é igual a um. Esse aumento se dá principalmente às custas da fração alveolar na CRF, principal reservatório de oxigênio do corpo[8,18]. Essa, associada a VO_2 e débito cardíaco, é responsável pela disponibilidade de O_2 ao paciente[8].

Pré-oxigenação, a despeito dos benefícios, também pode contribuir para a ocorrência de dessaturação da oxihemoglobina. Microatelectasias e distúrbio da relação ventilação/perfusão (V/Q) são documentados durante indução de anestesia sob diferentes FiO_2. Manobras de recrutamento alveolar e utilização de pressão expiratória final na via aérea (PEEP) podem reverter e prevenir, respectivamente, a ocorrência daqueles eventos[7,8]. Outras estratégias preventivas, como oxigenação apnéica, também vem sendo estudadas, mas não se sabe ainda qual técnica é a ideal[20,21].

Uma variação de ventilação não invasiva, a Pressão Positiva Contínua na Via Aérea (CPAP) é um modo ventilatório no qual o paciente respira espontaneamente através de um circuito pressurizado[22]. Em pacientes portadores de apneia obstrutiva do

sono, na qual seu uso já é bem estabelecido, foram evidenciados benefícios como melhora da sonolência e gravidade da doença, melhora dos desfechos cardiovasculares, além de redução na pressão arterial, e efeitos adicionais indiretos como melhora na resistência insulínica em não diabéticos[23-25].

Do ponto de vista ventilatório, seus benefícios são demonstrados pela melhora na troca gasosa alveolar, minimização da formação de atelectasia e aumento tanto da capacidade residual funcional quanto do volume corrente[22]. Melhoras na saturação periférica de oxigênio e no pico de fluxo respiratório e redução tanto da frequência quanto do trabalho respiratório já foram evidenciados em pacientes durante crise asmática[26].

Na população pediátrica, a aplicação do CPAP é amplamente estudada em pacientes com bronquiolite como alternativa à ventilação mecânica controlada em decorrência de seus efeitos nas pequenas vias aéreas (abertura alveolar, prevenção de atelectasia e aumento da capacidade residual funcional)[27,28].

Ensaio clínico randomizado demonstrou a realização do CPAP no setor de emergência de quatro hospitais na área rural de Gana. A técnica foi aplicada por enfermeiras locais treinadas por uma equipe norte-americana. Os 69 pacientes tinham entre três meses a cinco anos de vida com desconforto respiratório secundário a pneumonia, sepse, malária ou anemia severa coletados num período de quatro meses. As crianças foram então divididas em dois grupos: 1) os que recebiam CPAP logo após a admissão e 2) os que recebiam CPAP uma hora mais tarde, todos tendo seus sinais vitais medidos a cada 20 minutos durante duas horas. Os resultados mostraram benefício a todas as crianças através da redução da frequência respiratória, sendo aqueles mais

significativos estatisticamente (0,001 *vs*. 0,01) nos que receberam CPAP precocemente[29].

Existe evidência de que a CPAP pode ser eficiente em minimizar os efeitos deletérios da pré-oxigenação sob altas FiO_2 através da manutenção do volume pulmonar[7]. Seu uso na ventilação durante a indução de anestesia geral ainda necessita de estudos bem conduzidos para sustentar sua prática como rotina, mas pesquisas em adultos mostram resultados encorajadores[30,31].

Em ensaio clínico indiano, randomizado, duplamente encoberto, envolvendo 40 pacientes sem comorbidades, candidatos a cirurgia de grande porte, foram significativos o prolongamento do tempo de apneia antes da ocorrência de dessaturação e valores superiores de PaO_2 naqueles que receberam CPAP durante a indução anestésica. O uso de CPAP também reduziu o tempo de retorno ao valores basais normais de saturação após apneia[30].

O uso de CPAP também esteve relacionado a valores superiores de PaO_2 e inferiores de pressão arterial de dióxido de carbono ($PaCO_2$). Esses resultados foram obtidos em ensaio clínico realizado na Suécia com 44 pacientes obesos com índice de massa corporal (IMC) maior que $35kg/m^2$ submetidos a *by-pass* gástrico, utilizando ou não CPAP na indução da anestesia. Não ocorreram episódios de hipoxemia nos pacientes expostos à intervenção, diferentemente daqueles que não utilizaram a técnica de pressão positiva contínua[31].

Baseado no exposto, fica clara a necessidade de se realizar estudos bem conduzidos na população pediátrica. Assim, o objetivo desse estudo foi determinar a efetividade do CPAP durante a indução anestésica em prolongar o tempo de apneia

seguro (tempo até que a SpO_2 caia a 95%) em crianças submetidas a anestesia geral para cirurgia eletiva.

II. HIPÓTESES

2.1. HIPÓTESE PRIMÁRIA

- O uso de CPAP na ventilação pulmonar de pré-escolares durante a indução de anestesia geral para cirurgia eletiva prolonga o tempo de apneia seguro.

2.2. HIPÓTESES SECUNDÁRIAS

- Valores de saturação de oxihemoglobina na oximetria de pulso (SpO_2) em pacientes apnéicos em períodos semelhantes durante indução anestésica são maiores naqueles que utilizarem CPAP;

- Tempo para recuperação dos níveis normais de SpO_2 após período de apneia é menor em pacientes que utilizarem CPAP;

- A frequência de complicações é menor em pacientes que utilizarem CPAP;

- A frequência de queda da SpO_2 a 95% é menor entre os pacientes do grupo CPAP.

III. OBJETIVOS

3.1. OBJETIVO GERAL

Determinar a efetividade do CPAP durante a indução anestésica em prolongar o tempo de apneia seguro (tempo até que a SpO_2 caia a 95%) em crianças submetidas a anestesia geral para cirurgia eletiva.

3.2. OBJETIVOS ESPECÍFICOS

Em crianças submetidas a anestesia geral para cirurgia eletiva que foram submetidas durante a indução anestésica a ventilação com CPAP ou com circuito circular padrão, comparar:

DESFECHO PRIMÁRIO:

- O tempo entre o início da apneia e a queda da SpO_2 a 95% (tempo de apneia seguro).

DESFECHO SECUNDÁRIO:

1. Os valores de SpO_2 durante a indução anestésica em diferentes momentos;
2. O tempo para recuperação da SpO_2 pré-apneia;
3. O tempo de apneia seguro apenas entre os pacientes em que houve queda da SpO_2 a 95%;
4. A frequência de complicações;
5. A frequência de queda da SpO_2 a 95%.

IV. MÉTODOS

4.1. DESENHO DO ESTUDO

Ensaio clínico randomizado, fase III, paralelo, em pacientes pediátricos submetidos a cirurgias eletivas.

4.2. LOCAL DO ESTUDO

O estudo foi realizado no bloco cirúrgico do Hospital das Clínicas da Universidade Federal de Pernambuco Professor Romero Marques (HC-UFPE).

O serviço de cirurgia pediátrica do HC-UFPE realiza entre 15-20 cirurgias por semana em caráter eletivo; a equipe é composta por seis cirurgiões e três médicos residentes; e dispõe de uma sala no bloco cirúrgico em quatro turnos semanais nos quais realiza desde cirurgia neonatal até procedimentos em pacientes de 18 anos.

4.3. PERÍODO DO ESTUDO

O estudo foi realizado no período de março de 2018 a maio de 2019.

4.4. POPULAÇÃO DO ESTUDO

Pacientes pediátricos pré-escolares submetidos a cirurgia eletiva no bloco cirúrgico do HC-UFPE.

4.5. AMOSTRA

4.5.1. AMOSTRAGEM

Foi obtida uma amostra não probabilística de conveniência, composta pelas crianças em fase pré-escolar que seriam submetidas a anestesia geral para cirurgias eletivas, obedecendo aos critérios de inclusão e exclusão do estudo.

4.5.2. TAMANHO DA AMOSTRA

O cálculo do tamanho da amostra foi realizado no programa Openepi, versão 3.01 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Versão. www.OpenEpi.com, atualizado em 06/04/2013, acessado em 11/07/2017), usando diferença de médias. O primeiro parâmetro utilizado foi a média de tempo em apneia que os pacientes expostos à intervenção levaram para atingir uma saturação de oxigênio na oximetria de pulso de 95% (166 ± 47 segundos)[21]. O segundo parâmetro foi a média de tempo em apneia que os pacientes não expostos à intervenção levaram para atingir uma saturação de oxigênio na oximetria de pulso de 95% (131 ± 39 segundos)[21]. Considerando um nível de significância de 5% e um poder de 90%, seriam necessários 64 pacientes (32 em cada grupo). Entretanto, prevendo-se eventuais perdas por exclusão pós-randomização (em torno de 10%), esse número foi aumentado para 72 (36 em cada grupo).

4.5.3. PROCEDIMENTO PARA RANDOMIZAÇÃO

A tabela de randomização foi gerada no computador, utilizando-se o programa *Random Allocation Software* 1.0.0 (M. Saghaei, MD., Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran). Após a randomização, em blocos de 8, foram então preparados envelopes opacos numerados sequencialmente de 1 a 72 de acordo com a tabela de números randômicos. Foi respeitada a ocultação da alocação.

4.6. CRITÉRIOS E PROCEDIMENTOS PARA SELEÇÃO, CAPTAÇÃO E ACOMPANHAMENTO DOS PARTICIPANTES

4.6.1. CRITÉRIOS DE INCLUSÃO

- Crianças em idade pré-escolar;
- Estado físico I ou II segundo a Sociedade Americana de Anestesiologistas (ASA);

- Crianças submetidas a anestesia geral para cirurgia eletiva;

4.6.2. CRITÉRIOS DE EXCLUSÃO

- Doença pulmonar parenquimatosa pré-existente;
- Crianças cianóticas ou com saturação da oxihemoglobina menor que 95% antes da indução anestésica;
- História recente (<4 semanas) ou vigência de infecção do trato respiratório superior.

4.6.3. PROCEDIMENTOS PARA CAPTAÇÃO E ACOMPANHAMENTO DOS PARTICIPANTES

A captação dos participantes foi realizada por um pesquisador que não participou da coleta de dados. Ele ficou unicamente responsável por captar os participantes, aplicar os critérios de elegibilidade utilizando uma lista de checagem (Apêndice 1) e solicitar a assinatura do TCLE. Essa etapa aconteceu na admissão no bloco cirúrgico onde os pacientes e acompanhantes, vindos do ambulatório após pesagem, aguardavam a cirurgia. Posteriormente, era entregue ao pesquisador principal o envelope referente ao participante onde constava no interior o grupo a que ele foi alocado.

A alocação foi feita por envelopes sequencialmente numerados, de outra forma idênticos, selados, cada um contendo um papel de 2 polegadas por 2 polegadas com um código escrito (CPAP ou ABERTO) que designava o grupo intervenção ou o grupo Controle. Não havia diferenças detectáveis em tamanho ou peso entre os envelopes do grupo intervenção e os envelopes do grupo comparativo. Os envelopes eram opacos e abertos sequencialmente somente depois de escritas neles as informações referentes ao pacientes aos quais foram designados. A abertura do envelope ocorreu antes da entrada do paciente na sala de cirurgia para que o cenário do estudo fosse montado.

O pesquisador principal foi responsável por todo o procedimento juntamente com o anestesista responsável pela cirurgia. A coleta de dados por sua vez foi realizada por outro pesquisador responsável apenas pela coleta dos dados sem conhecimento do grupo a que o paciente seria alocado (sistema de CPAP foi selecionado antes da entrada do aluno na sala para coleta).

Foi preenchido um fluxograma (CONSORT) com o progresso do estudo ao longo das fases de um estudo de intervenção em paralelo de dois grupos (seleção dos participantes, alocação de intervenção, acompanhamento e análise de dados) (Figura 1).

Todos os prontuários dos participantes envolvidos no estudo foram identificados no formulário de coleta (Apêndice 3) contendo o nome da pesquisa, número do registro, número de identificação da paciente no estudo e o grupo em que foi alocado.

4.7. FLUXOGRAMA DE CAPTAÇÃO E ACOMPANHAMENTO DOS PARTICIPANTES

O fluxograma de captação e acompanhamento dos participantes da pesquisa está demonstrado na figura 1, abaixo.

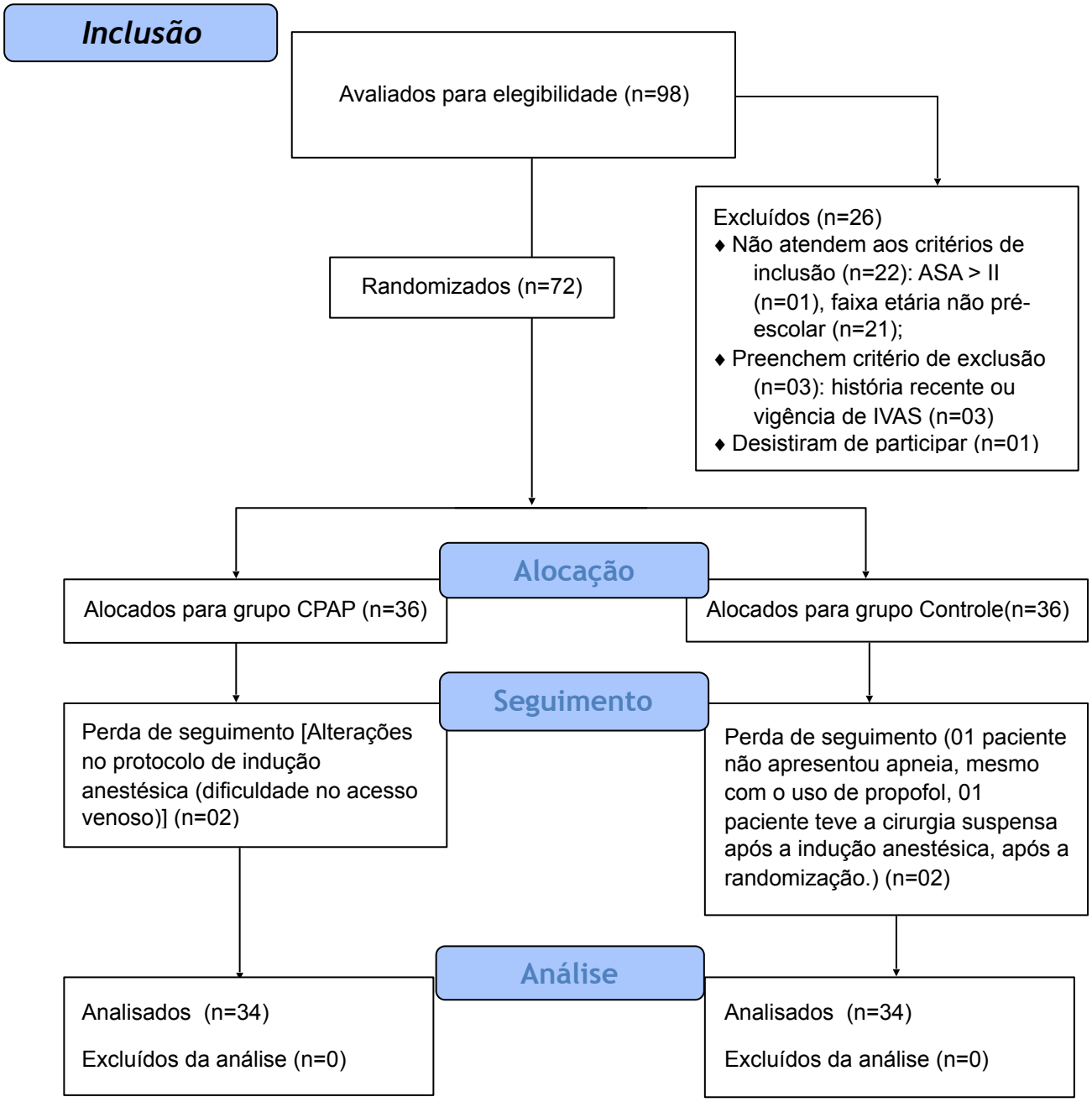

Figura 1. Fluxograma de captação e acompanhamento dos participantes

4.8. TERMOS, VARIÁVEIS E CONCEITOS

4.8.1. VARIÁVEIS DE CONTROLE (PARA CARACTERIZAÇÃO DA AMOSTRA)

- Idade
- Peso
- Sexo
- Estado físico segundo a ASA
- Tipo de cirurgia

4.8.2. VARIÁVEL INDEPENDENTE

- Uso de CPAP

4.8.3. VARIÁVEIS DEPENDENTES

- Tempo entre o início da apneia e a queda da saturação periférica da oxihemoglobina (SpO_2) a 95% ou tempo máximo de observação de 300 segundos (Tempo 1);
- Tempo para recuperação da SpO_2 a níveis pré-apneia (Tempo 2);
- Tempo entre o início da apneia e a queda da SpO_2 a 95% apenas entre os pacientes em que houve queda da SpO_2 a 95% (Tempo 3);
- Saturação de oxihemoglobina na oximetria de pulso durante a indução anestésica em diferentes momentos;
- Frequência de complicações: laringoespasmo, hipoxemia, bradicardia, parada cardiorrespiratória, morte;
- Frequência de queda da SpO_2 a 95%.

4.8.4. DEFINIÇÃO DE TERMOS E VARIÁVEIS

- Apneia central - Cessação transitória da respiração por qualquer duração usualmente acompanhada de bradicardia e/ou cianose[32]. Foi considerada apneia a parada dos movimentos respiratórios associada a ausência de leitura da capnografia. A apneia foi induzida com a injeção de 3,5mg/kg de propofol;
- Ventilação pulmonar - Volume total de gás inspirado ou expirado na unidade de tempo[33];
- Pré-escolar - Consideramos as crianças cuja faixa etária compreendia dos dois anos completos aos sete anos incompletos;
- Oxihemoglobina - Composto formado pela combinação de hemoglobina e oxigênio no qual este último se liga diretamente ao ferro sem causar mudança deste do estado ferroso para o férrico;
- Oximetria de pulso - Determinação da saturação da oxihemoglobina do sangue através de eletrodos ligados a alguma parte translucente do corpo (dedo, lobo da orelha, dobra da pele)[34];
- Laringoespasmo - Complicação respiratória decorrente do fechamento reflexo da glote mais comum em crianças durante anestesia superficial[35]. Variável dependente, qualitativa, nominal, dicotômica, tendo como categorias sim ou não;
- Anestesia geral - Estágio transitório de inconsciência induzido por fármacos através de suas ações em receptores moleculares[1];

- Doença pulmonar parenquimatosa - Grupo diverso de doenças pulmonares caracterizado inicialmente por inflamação dos alvéolos que se extende para o interstício, levando a fibrose pulmonar difusa. Foi considerada a partir do relato do responsável pelo paciente ou por exame complementar presente no prontuário ou apresentado ao pesquisador no dia da cirurgia;
- Cianose - Coloração azulada ou púrpura da pele e mucosas devido a aumento da hemoglobina desoxigenada no sangue ou por um defeito estrutural da molécula de hemoglobina;
- Infecção do trato respiratório superior - Invasão do trato respiratório superior do hospedeiro por um patógeno, normalmente vírus ou bactéria. As principais doenças classificadas nesse grupo são rinofaringite viral, sinusite aguda, faringoamidalite aguda estreptocócica e laringite viral aguda. A rinofaringite viral aguda é a representante mais comum desse grupo e é caracterizada por dor de garganta, coriza, obstrução nasal, espirros, tosse seca e febre de intensidade variável[36]. Foi considerada a partir do relato do responsável pelo paciente;
- CPAP - Modo ventilatório no qual o paciente respira espontaneamente através de um circuito pressurizado contra um resistor de limiar que mantém uma determinada pressão durante tanto na inspiração quanto na expiração[37]. Foi utilizado o circuito do aparelho de anestesia (Carestation™ 620, Datex-Ohmeda, Inc. 3030 Ohmeda Drive PO Box 7550 Madison, WI 53707-7550 USA) em modo circular com traquéias próprias para crianças com ajuste da válvula *Adjustable Pressure Limiting* (APL) para uma pressão de 10cmH_2O. Variável independente, qualitativa, nominal, dicotômica, tendo como categorias sim ou não;

- Tempo entre o início da apneia e a queda da saturação periférica da oxihemoglobina (SpO_2) a 95% ou tempo máximo de observação de 300 segundos (Tempo 1) - Variável dependente, quantitativa, numérica, contínua, medida em segundos através de cronômetro (iPhone 7 Plus 12.3.1, One Apple Park Way Cupertino, CA 95014 USA);
- Tempo para recuperação da SpO_2 a níveis pré-apneia (Tempo 2) - Variável dependente, quantitativa, numérica, contínua, medida em segundos através de cronômetro (iPhone 7 Plus 12.3.1, One Apple Park Way Cupertino, CA 95014 USA);
- Tempo entre o início da apneia e a queda da SpO_2 a 95% apenas entre os pacientes em que houve queda da SpO_2 a 95% (Tempo 3) - Variável dependente, quantitativa, numérica, contínua, medida em segundos através de cronômetro (iPhone 7 Plus 12.3.1, One Apple Park Way Cupertino, CA 95014 USA);
- Saturação de oxihemoglobina na oximetria de pulso durante a indução anestésica em diferentes momentos - Variável dependente, quantitativa, numérica, discreta, medida em pontos percentuais por oxímetro de pulso;
- Dessaturação até o tempo máximo de cinco minutos - Variável dependente, qualitativa, nominal, dicotômica, tendo como categorias sim ou não. Foi considerada dessaturação quando a leitura na oximetria de pulso registrou 95% até o tempo máximo de cinco minutos (300 segundos) através de cronômetro (iPhone 7 Plus 12.3.1, One Apple Park Way Cupertino, CA 95014 USA);
- Idade - Variável quantitativa, numérica, contínua, medida em meses completos de vida a partir da data de nascimento;

- Peso - Variável quantitativa, numérica, contínua, medida em gramas. Foi considerado o peso medido no ambulatório de pediatria na admissão hospitalar do paciente no dia da cirurgia;
- Sexo - Variável qualitativa, nominal, dicotômica, tendo como categorias masculino e feminino;
- Estado físico segundo a ASA - Estado físico do paciente baseado na presença/ ausência de doença nos pacientes ou em alterações fisiológicas não patológicas, bem como na qualidade do controle das morbidades[38]. Variável ordinal cujas categorias são numeradas em algarismos romanos de I a VI, sendo os estados I, ausência de doença sistêmica, e II, doença sistêmica controlada[39]. A classificação do estado físico do paciente foi feita antes da admissão do paciente no bloco cirúrgico e da alocação oculta.

4.9. **PROCEDIMENTOS, TESTES, TÉCNICAS E EXAMES**

4.9.1. **REALIZAÇÃO DA ANESTESIA**

Os pacientes selecionados para o estudo foram admitidos na sala de operação e receberam monitorização habitual (cardioscópio, oxímetro, pressão arterial não invasiva e capnografia).

A indução inalatória foi realizada através de máscara facial acoplada ao sistema circular do aparelho de anestesia (Carestation™ 620, Datex-Ohmeda, Inc. 3030 Ohmeda Drive PO Box 7550 Madison, WI 53707-7550 USA), fixada ao paciente com auxílio de faixa elástica, utilizando sevoflurano a 8%, fração inspirada de oxigênio de 60% sob um fluxo de gases frescos de 4l/min (2l de oxigênio e 2l de ar comprimido) até perda do reflexo palpebral. A concentração do anestésico era então reduzida para 4%.

Após a adequada ventilação ser constatada através do correto posicionamento da máscara facial e de curva de capnografia presente, foi obtido acesso venoso periférico com cateter venoso número 20, 22 ou 24G para hidratação e infusão de propofol na dose de 3,5mg/kg para induzir apneia nos pacientes de ambos os grupos.

4.9.2. Realização do CPAP

Os pacientes foram submetidos logo após a monitorização à técnica descrita nos envelopes entregues na entrada do bloco cirúrgico.

No grupo CPAP, este foi aplicado no aparelho de anestesia, utilizando um sistema circular. Esse sistema consiste de dois tubos corrugados acoplados numa extremidade a uma peça em Y, conectada à máscara facial do paciente, e na outra extremidade ao aparelho de anestesia que, além de fornecer o fluxo de gases frescos, possui um absorvedor de gás carbônico. Esse último além de possibilitar o sistema ser circular por retirar o CO_2 do ar fornecido ao paciente, aquece e umidifica a mistura gasosa. Uma válvula limitadora de pressão [válvula *Adjustable Pressure Limiting* (APL)], que impede a perda de gases pelo sistema paciente-aparelho quando fechada, é parte integrante do aparelho de anestesia. Aquela possui diversas marcações (0-70cmH_2O), é manipulada manualmente e pode estar aberta (0cmH_2O), ou seja, sem que nenhuma pressão seja fornecida à via aérea do paciente, ou fechada. Na posição fechada, havia uma pressão positiva contínua sendo fornecida à via aérea do paciente. A pressão que foi utilizada neste grupo foi de 10cmH_2O. Nos pacientes do grupo Controle, o sistema permaneceu com a válvula na posição aberta, ou seja, 0cmH_2O, sendo todos os demais procedimentos realizados de maneira semelhante aos dos pacientes do grupo CPAP.

Em ambos os grupos, os pacientes ventilaram espontaneamente desde o princípio com a técnica definida no momento da alocação.

4.10. PROCEDIMENTOS PARA COLETA DOS DADOS

4.10.1. INSTRUMENTO DE COLETA DE DADOS

Os dados foram coletados utilizando um formulário padronizado, pré-codificado para entrada dos dados no computador (Apêndice 3). As informações das variáveis categóricas foram pré-codificadas e as variáveis contínuas expressas em seu próprio valor numérico e só no momento da análise os resultados de algumas destas foram categorizados.

Esses formulários estão devidamente armazenados em pastas de arquivo específicos, antes e depois da digitação e análise, sob responsabilidade do próprio pesquisador, que os preencheu em diferentes momentos, antes, durante e após o procedimento cirúrgico.

4.10.2. COLETA DE DADOS

Os dados foram coletados por um pesquisador independente que esteve presente na sala de cirurgia, preencheu o formulário com os dados de identificação do paciente e as variáveis de estudo e não interferiu no procedimento anestésico realizado.

O tempo a partir do momento da cessação dos movimentos respiratórios e decaimento da curva de capnografia foi cronometrado (iPhone 7 Plus 12.3.1, One Apple Park Way Cupertino, CA 95014 USA). A medição aconteceu até o registro na oximetria de pulso do valor de 95% ou por um período máximo de cinco minutos. Ventilação assistida era então instituída (no grupo Sistema Aberto, a válvula APL era fechada manualmente até o valor de 10cmH_2O). Houve nesse momento nova cronometragem do

tempo até leitura na oximetria de pulso do valor de 100% ou do valor obtido imediatamente antes do início da apneia.

4.11. **PROCESSAMENTO E ANÁLISE DOS DADOS**

4.11.1. **PROCESSAMENTO DOS DADOS**

A digitação no banco de dados específico criado no programa Excel foi realizada duas vezes, em épocas e por pessoas diferentes, obtendo-se ao final uma listagem para correção de eventuais erros de digitação, com supervisão do próprio pesquisador.

Em se constatando inconsistências ou ausência de dados por ocasião da revisão das listagens, seriam consultados os formulários arquivados correspondentes de acordo com o número de registro dos pacientes.

Ao término da entrada de todos os formulários no banco de dados, foi realizada a revisão final, completando-se os dados ausentes pelos processos acima mencionados. O banco de dados definitivo assim criado foi, então, utilizado para análise estatística no programa STATA, sendo ainda submetido a testes de consistência e limpeza das informações, gerando-se cópias de segurança.

4.11.2. **ANÁLISE DOS DADOS**

A análise dos dados foi realizada pelo pesquisador e pelo estatístico responsável, utilizando o programa STATA®12.1 SE (StataCorp, 4905 Lakeway Drive College Station, Texas 77845 USA).

A análise estatística descritiva foi realizada através de medidas de tendência central e de dispersão para as variáveis quantitativas e através distribuição de frequências para as variáveis qualitativas.

Para as variáveis categóricas foram realizados os testes qui-quadrado de associação com correção de Yates e o teste exato de Fisher quando indicado (um dos valores esperados menor que cinco). Também foi calculada a razão de risco (RR) como medida do risco relativo e o seu intervalo de confiança a 95%. À categoria de referência foi atribuído o risco padrão de 1,0.

Em relação às variáveis numéricas, foi aplicado o teste de Shapiro-Wilk para testar sua normalidade. Como a amostra apresentou distribuição normal, foi utilizado o teste paramétrico (t de *Student*) além de média e desvio-padrão como medida de dispersão.

Uma análise de sobrevivência foi conduzida, levando em consideração o tempo até a queda da $SatO_2$ a 95%. A este respeito, as taxas de sobrevivência foram calculadas usando o método de Kaplan-Meier e as curvas de sobrevivência foram comparadas usando o teste de log-rank (Mantel-Cox). Foi calculada também a probabilidade acumulada para avaliar as chances que cada individuo do estudo tinha de atingir uma SpO_2 de 95% entre o início do estudo e um determinado tempo (neste caso até 300 segundos).

Além disso, foram construídas curvas com as médias das SpO_2 medidas nos períodos de intervalo de 30 segundos mediante o ajuste por um modelo de regressão para dados correlacionados que também avaliou a significância do tempo, grupo e a interação entre eles. As comparações de médias entre os dois grupos, em um dado tempo, foram realizadas com o teste de Wald. Foi considerado significante um $p<0.05$.

4.12. **ASPECTOS ÉTICOS**

A pesquisa respeitou os direitos humanos e os princípios da bioética (Autonomia, Não-Maleficência, Beneficência, Justiça e Eqüidade). O sigilo e a confidencialidade na coleta e arquivo dos dados colhidos foram respeitados.

Os termos da resolução nº 466 de 12 de dezembro de 2012 do Conselho Nacional de Saúde para pesquisa em seres humanos foram seguidos assim como a declaração de Helsinque. Além disso, o projeto foi submetido à apreciação do Comitê de Ética em Pesquisa em Seres Humanos da instituição proponente e aprovado pelo mesmo (CAAE: 79591417.0.0000.5201, parecer nº 2.457.340), os dados somente foram colhidos após tal submissão e aprovação e as crianças do estudo somente foram incluídas após os responsáveis assinarem o Termo de Consentimento Livre e Esclarecido (TCLE, Apêndice 2).

O estudo foi registrado no ClinicalTrials.gov sob o número NCT03432390 e não ofereceu riscos ou desconfortos adicionais, além daqueles inerentes ao próprio procedimento anestésico-cirúrgico, assim como também não foram relatados na literatura efeitos adversos que contraindicassem o uso de CPAP durante a indução. Ao contrário, os poucos estudos existentes referiam melhora respiratória com o uso desta intervenção. Todos os procedimentos da pesquisa foram realizados por profissionais treinados e capacitados, tanto para a realização da anestesia pediátrica, como para a aplicação do CPAP.

O TCLE participou aos responsáveis todas as informações com relação às vantagens e às desvantagens do uso das duas técnicas; enfatizou que não seria realizado nenhum procedimento já não utilizada de rotina pela equipe; além de que nele constava o direito de se recusarem a participar do estudo, bem como a garantia de assistência

àqueles que não aceitassem, sem haver ressarcimento por parte da instituição, nem por parte dos pesquisadores. Estes se comprometeram a publicar o estudo, independentemente dos resultados obtidos.

4.13. **CONFLITOS DE INTERESSE**

Esta pesquisa esteve livre de conflito de interesses, particular ou institucional. Não houve financiamento por parte de indústria farmacêutica ou de representantes de nenhum objeto de pesquisa utilizado.

V. RESULTADOS

Os resultados dessa dissertação foram enviados para publicação. Artigo submetido à revista *Anesthesiology*, fator de impacto 6.523, Qualis CAPES A1 (instruções aos autores encontram-se disponíveis no anexo 2).

Continuous positive airway pressure during induction of general anesthesia in children: a randomized clinical trial

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Summary statement: Continuous positive airway pressure during induction of anesthesia was shown to effectively increase safe apnea time in children submitted to general anesthesia for elective surgery.

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Abstract

Background: Episodes of desaturation during induction of anesthesia are more likely in children. Continuous positive airway pressure (CPAP) is a type of ventilation that can improve alveolar gas exchange at this time, minimizing the incidence of atelectasis and increasing functional residual capacity. This study aimed to evaluate the effectiveness of CPAP during induction of anesthesia in increasing safe apnea time (time in apnea until hemoglobin saturation falls to 95%).

Methods: Phase III randomized clinical trial with 68 children divided into two parallel groups of 34 (CPAP and controls). Preschool-aged children, evaluated as physical status I or II according to the American Society of Anesthesiology physical status classification system and who were submitted to elective surgery under general anesthesia, were included in the study. The main outcome measures were: (1) time between the beginning of apnea and the fall in peripheral oxygen saturation (SpO_2) to 95% (T1); (2) time until recovery of SpO_2 to pre-apnea levels (T2) and (3) the frequency of a decrease in SpO_2 to 95%.

Results: T1 was greater in the CPAP group compared to the control group: 227.65 ± 84.74 seconds versus 133.68 ± 70.39 seconds; $p<0.0001$. There was no difference in T2 between the groups: 38.65 ± 49.07 versus 43.12 ± 60.64; $p=0.7945$. In the survival analysis, survival (likelihood of each patient in the study reaching SpO_2 to 95% within a given time) was greater in the CPAP group compared to the control group (log-rank test; $p=0.000$). Saturation remained above 95% in more patients in the CPAP group: 17/34

(50%) versus 2/34 patients (5.9%); RR=0.5313; 95%CI: 0.3757-0.7512; p<0.000. Repeated measures saturation values were higher in the CPAP group.

Conclusions: CPAP during induction of anesthesia effectively increased safe apnea time in children submitted to general anesthesia for elective surgery.

Keywords: continuous positive airway pressure; hypoxia; general anesthesia; pediatrics.

Clinical trial registration at ClinicalTrials.gov: NCT03432390

Introduction

General anesthesia causes numerous changes to the respiratory system. In particular, it increases the likelihood of airway obstruction and collapse. Following induction of anesthesia, there is a reduction in functional residual capacity resulting from a loss in muscle tone and in pulmonary compliance, the formation of atelectasis in the dependent lung zones and changes in the movements of the diaphragm. These alterations can result in an increase in resistance and closure of the small airways, and changes in the ventilation/perfusion (V/Q) ratio.[1-4]

During the apnea that follows induction of anesthesia, oxygen reserves are consumed and can lead to hypoxemia.[5] Pediatric patients are more likely to experience episodes of desaturation during induction (4-10%).[5-8] This is particularly due to their anatomical characteristics (proportionally large head and tongue, hypertrophy of the tonsils and adenoids, smaller and narrower hypopharynx, higher larynx, slanted vocal cords, epiglottis folded into an inverted "U" shape, and smaller airway radius) and to their physiological characteristics (lower functional residual capacity, greater oxygen consumption, and greater carbon dioxide [CO_2] production). Altogether, these factors contribute towards triggering and maintaining hypoxemia,[7,9-11] rendering children more vulnerable to severe complications such as cardiorespiratory arrest and death.[7]

Pre-oxygenation with 100% oxygen allows safe apnea time (the period of time until oxyhemoglobin desaturation) to be prolonged, and is often used to prevent

hypoxemia[7,9,12]. Nevertheless, despite the benefits, pre-oxygenation under different fractions of oxygen, particularly with pure oxygen (100%), can contribute to the occurrence of micro-atelectasis and changes in the V/Q ratio during induction of anesthesia. Alveolar recruitment maneuvers and the use of positive end-expiratory pressure can reverse and prevent the occurrence of these events.[4,5] Other preventive strategies are also being evaluated; however, the ideal technique has yet to be established.[13,14]

Continuous positive airway pressure (CPAP) is a type of ventilation in which the patient breathes spontaneously through a pressurized circuit. Its benefits include improved alveolar gas exchange, a reduction in the incidence of atelectasis and increased functional residual capacity and tidal volume.[15] In the pediatric population, the application of CPAP has been widely studied in patients with bronchiolitis as an alternative to controlled mechanical ventilation in view of its effects on the small airways (alveolar opening, prevention of atelectasis and increased functional residual capacity).[16,17] However, evidence for its use during the induction of general anesthesia is sparse and further, well-conducted studies are required to support its use as routine practice.[18,19]

The objective of the present study was to evaluate the effectiveness of CPAP during the induction of anesthesia in increasing safe apnea time, i.e. time in apnea until hemoglobin saturation falls to 95%, in children submitted to general anesthesia for elective surgery.

Materials and Methods

This was a phase III, parallel group, randomized clinical trial involving 68 children submitted to elective surgery at the Federal University of Pernambuco's Teaching Hospital between March 2018 and May 2019. The internal review board of the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP) approved the protocol under reference CAAE: 79591417.0.0000.5201 and the study was registered at ClinicalTrials.gov under reference NCT03432390. The parents or guardians of all the participating children gave their written informed consent.

Preschool-aged children evaluated as physical status I or II according to the American Society of Anesthesiology physical status classification system and who were to be submitted to general anesthesia for elective surgery in the hospital's surgical center were eligible for the study. The exclusion criteria were preexisting parenchymal lung disease, cyanosis or hemoglobin saturation <95% prior to induction of anesthesia, and a current upper respiratory tract infection or a history of one in the preceding four weeks.

The outcome measures were: (1) time between the beginning of apnea and the fall in peripheral oxygen saturation (SpO_2) to 95% or a maximum observation time of 300 seconds (T1); (2) time until recovery of SpO_2 to pre-apnea levels (T2); (3) time between the beginning of apnea and the fall in SpO_2 to 95% only in those patients in whom SpO_2 fell to 95% (T3); (4) the proportion of patients in whom SpO_2 fell to 95%; and (5) SpO_2

values every ten seconds. Since T1 was recorded until SpO_2 reached 95% or up to a maximum of 300 seconds, T1 values could not exceed five minutes.

Sample size was calculated using OpenEpi, version 3.01, taking the difference in means between two parameters into consideration. The first parameter used was the reported mean time in apnea that the patients exposed to the intervention took to reach oxygen saturation of 95% at pulse oximetry (166 ± 47 seconds).[14] The second parameter was the mean time in apnea that the patients not exposed to the intervention took to reach oxygen saturation of 95% at pulse oximetry (131 ± 39 seconds).[14] Considering a significance level of 5% and a power of 90%, 64 patients would be required, 32 in each group. However, to compensate for any losses following randomization (predicted at around 10%), this number was increased to 72 patients: 36 in each group.

The patients enrolled in the study were randomized to one of two groups, the CPAP group or the control group. Randomization was performed using concealed allocation, with numbers generated in blocks of 8 by the Random Allocation Software program. Recruitment was carried out in the surgical ward, while pediatric patients accompanied by their parents/guardians awaited surgery. The envelopes were opened sequentially only after the checklists with the data on the patient allocated to that particular envelope were attached and before the child went into the operating room to ensure compliance with the protocol. A research assistant, who had no knowledge of the group to which the patient had been allocated, performed data collection.

The patients selected for the study were admitted to the operating room and monitored according to the routine hospital procedures (cardioscopy, pulse oximetry, non-invasive blood pressure monitoring and capnography). Inhalational induction was performed using a facemask connected to the circle system of the anesthesia machine (Carestation 620, Datex-Ohmeda, Inc. Madison, WI) and attached to the patient by an elastic strap. Sevoflurane at 8% was used, with fraction of inspired oxygen of 60.5% under a fresh gas flow of 41/min (21 of oxygen and 21 of compressed air) until loss of eyelid reflex. The concentration of anesthesia was then reduced to 4%. Adequate ventilation was confirmed by checking if it produced a capnographic waveform and if the facemask was placed correctly. Peripheral intravenous access was then obtained in the patients in both groups using a venous catheter number 20, 22 or 24G for hydration and infusion of propofol at a dose of 3.5 mg/kg or sufficient to induce apnea.

In the patients in the CPAP group, the adjustable pressure-limiting valve was manipulated manually to 10 cmH_2O to allow this level to be provided to the patient. In the control group, the valve was left in the open position, i.e. 0 cmH_2O. In both groups, the patients breathed spontaneously from the onset, with the technique to be used being defined at the time of randomization. The anesthetist accompanying the patient was present throughout the anesthetic procedure in all cases and the patient remained under his/her care when the study ended. T1 was timed using an Iphone 7 Plus 12.3.1 (Apple Inc., Cupertino, CA) starting when respiratory movements stopped and the capnographic waveform dropped, and pulse oximetry reading was recorded at 10-second intervals. When SpO_2 reached 95%, assisted ventilation was then instituted (in

the open system group, the adjustable pressure-limiting valve was closed manually to the level of 10 cmH_2O). At that time, T2 was measured. In addition, any adverse events occurring during the study period were observed and recorded.

Statistical analysis

Data analysis was performed using STATA, version 12.1 SE (StataCorp, College Station, TX). The descriptive statistical analysis was carried out using measures of central tendency and dispersion for the quantitative variables and frequency distribution for the qualitative variables. The chi-square test of association with Yates correction was used for the categorical variables, with Fisher's exact test being applied whenever appropriate (i.e. one of the expected values was below five). Risk ratios (RR) were also calculated as measures of relative risk, together with their 95% confidence intervals. The standard risk of 1.0 was attributed to the reference category. The Shapiro-Wilk test confirmed the normality of distribution of the numerical variables. Therefore, Student's parametric t-test was used, with results shown as means and standard deviations as the measure of dispersion. Survival analysis was conducted on the time until the fall in SpO_2 to 95%. Survival rates were calculated using the Kaplan-Meier method and the survival curves were compared using the log-rank test. Cumulative probability was also calculated to evaluate the likelihood of each patient in the study reaching desaturation within a given time (in this case 300 seconds). In addition, a curve was constructed with the mean SpO_2 measurements at the 30-second intervals by adjusting a regression model for correlated data that also evaluated the significance of time, group and the interaction

between them. The means were compared between the two groups at a given moment using the Wald test. Statistical significance was defined as p-values <0.05.

Results

Ninety-eight patients were screened for participation in the study. Of these, 72 were included. There were four losses to follow-up, two in each group. Therefore, the final analysis included 68 patients, 34 in the CPAP group and 34 in the control group (Figure 1).

The groups were similar with respect to age, weight, sex and physical status. The most common types of surgery were herniorrhaphy (inguinal, bilateral or unilateral, umbilical and epigastric) and urological (circumcision, orchidopexy and hypospadias). There were also cases of combined surgery, in which different groups of surgery were performed concomitantly, e.g. herniorrhaphy associated with orchidopexy (Table 1).

When evaluating all the patients by considering a T1 of 300 seconds for those in whom SpO_2 did not drop to 95%, T1 was greater in the CPAP group compared to the control group: 227.65 ± 84.7 seconds, 95%CI: 198.08-257.21 versus 133.68 ± 70.39 seconds, 95%CI: 109.11-158.24; p<0.0001 (Table 2).

When only the patients in whom SpO_2 fell to 95% (n=49) were evaluated, no statistically significant difference in T2 was found between the groups: 38.65 ± 49.07 seconds in the CPAP group (95%CI: 13.42-63.87) versus 43.12 ± 60.64 seconds in the

control group (95%CI: 21.26-64.99); p=0.7945. However, the statistically significant difference persisted between the groups with respect to the time between the beginning of apnea and the fall in SpO_2 to 95% (T3) only for the patients in whom SpO_2 fell to 95%: 161.17 ± 61.91 seconds versus 123.28 ± 58.12 seconds; p=0.038 (Table 2).

Survival analysis conducted to evaluate the fall in SpO_2 to 95% showed that survival was greater in the intervention group compared to the control group (log-rank test, p=0.000) (Figure 2). In this case, survival referred to the fall in SpO_2 to 95%. The cumulative probability of maintaining SpO_2 values at pre-induction levels was 0.5 (50%) in the CPAP group and 0.05 (5%) in the control group at 300 seconds. Therefore, it is reasonable to conclude that the likelihood of a patient in the CPAP group reaching 300 seconds without a drop in SpO_2 was 50%, whereas the likelihood of a patient in the control group not experiencing desaturation up to 300 seconds was 5%.

Figure 3 shows the curve formed by the SpO_2 values every 30 seconds, with higher SpO_2 levels in the CPAP group compared to the control group (p=0.0004 for the intergroup interaction). This means that being in the CPAP group increased the likelihood of maintaining higher SpO_2 levels, with the changes in SpO_2 being directly associated with the group to which the patient belonged. This figure also shows the mean SpO_2 levels with their respective standard deviations, separately for each evaluation moment.

At the end of the observation period, more patients in the CPAP group had SpO_2 levels over 95%: 17/34 patients (50%) versus 2/34 patients (5.9%); RR = 0.5313; 95%CI: 0.3757-0.7512; $p<0.000$ (Table 2).

Discussion

CPAP successfully increased safe apnea time during induction of anesthesia. Repeated measures saturation values were greater in the CPAP group and more patients in this group had saturation levels over 95%. There was no difference between the groups regarding the time of saturation recovery to pre-apnea values. Survival analysis for a decrease in SpO_2 to 95% showed that survival was greater in the intervention group compared to the control group.

Induction of anesthesia becomes a critical moment in a surgical procedure when the loss of consciousness and apnea is accompanied by a loss of respiratory muscle tone, a reduction in functional residual capacity, air trapping and absorption atelectasis that alters pulmonary compliance.[4,20] Cessation of airflow to the small airways compromises the dynamics of pulmonary gas exchange and adds a further challenge in the need to recruit the more distal airways.

The principal sources of oxygen in the body of healthy patients are the blood, lungs and myoglobin, as well as oxygen diluted in the tissues. Depletion of these stocks depends on characteristics such as functional residual capacity and metabolic gas consumption.[6] The association of the supine position and the induction of anesthesia may cause functional residual capacity to fall by as much as 30%.[20] In pediatric patients, unlike adults, lung volume and capacity are directly related to weight, height and age, i.e. the younger and smaller the child, the lower his/her functional residual capacity.[21] Since

basal metabolic rate is increased in certain patients such as children, the imbalance between supply and consumption of oxygen means that the final result is an overall and progressive fall in oxygen levels in the body (hypoxic hypoxia). The fastest way for the anesthesiologist to deal with this situation is to apply techniques that increase functional residual capacity and, consequently, oxygen reserves in the lungs.

Pre-oxygenation is used to prevent hypoxemia[4,5,9,22,23] by increasing oxygen content and reducing alveolar nitrogen.[9,22] Pulmonary oxygen content can increase more than 6-fold in patients breathing a fraction of inspired oxygen (FiO_2) of 100%, although the increase in the remaining stores is not of the same magnitude.[9] However, simply providing high fractions of inspired oxygen could be harmful, since this would increase the likelihood of absorption atelectasis induced by the loss of alveolar stability due to denitrogenation.[4,21] So, a combination of offering adequate fractions of oxygen and maintaining functional residual capacity by delivering positive pressure appears to represent an alternative for satisfactory pre-oxygenation.

Different ways of performing pre-oxygenation have been described, either with bag-mask ventilation (ventilation with tidal volume, vital capacity, under positive pressure) or with the provision of some type of continuous, non-invasive positive pressure (CPAP, pressure support ventilation, with or without positive end-expiratory pressure, transnasal humidified rapid-insufflation ventilatory exchange).[22,23] Despite its well-established use, pre-oxygenation with only minute volume proved ineffective in almost one-third of 2,398 patients in an observational study.[24]

In the present study, the technique selected was CPAP, with the objective of maintaining the opening of the small airways and preserving functional residual capacity. This technique could be considered a type of apneic oxygenation since it provides a greater quantity of oxygen during apnea. This is achieved through an increase in the transpulmonary pressure gradient secondary to a continuous flow of gases capable of maintaining the alveoli open and increasing oxygen reserves in the lungs, avoiding or delaying the occurrence of hypoxemia. Together with this mechanical component, the greater oxygen pressure supplied improves CO_2 clearance by removing this gas from the distal airways.[25]

Mean safe apnea time was greater in the CPAP group compared to the control group. A study conducted in an adult population[26] reported similar results using different pressure in the CPAP (20 cmH_2O). That randomized clinical trial used a similar technique to the one used here in which CPAP was mounted directly onto the anesthetist's workstation. In our opinion, this was particularly important since the mixture of gases inhaled by the patient was warm and, in addition, practicality was greater, since it did not require the addition of any extra device to the setting.

Likewise, a clinical trial conducted in 2015[18] to evaluate the effect of applying CPAP of 5 cmH_2O during pre-oxygenation and induction of anesthesia in the period of apnea preceding the occurrence of clinically significant desaturation reported similar results to those found in the present study; however, the technique used was different. The

application of CPAP of 5 cmH_2O used the Mapleson A circuit with a final fixed positive end-expiratory pressure device for five minutes of pre-oxygenation with 100% oxygen.

In the study that used transnasal humidified rapid-insufflation ventilatory exchange for apneic oxygenation in pediatric patients, the results were similar to those found in the present study for the group of children of 2-5 years of age.[13]

A pilot study[27] analyzed the same parameter using a nasal cannula with oxygen flow introduced following pre-oxygenation with a facemask. The intervention was not significantly different insofar as safe apnea time was concerned, unlike the present study in which safe apnea time was longer with the use of CPAP.

A clinical trial whose intervention consisted of the use of CPAP together with pressure support ventilation at induction of anesthesia in obese patients[19] found that the arterial oxygen pressure (PaO_2) was greater in the intervention group at similar moments compared to those of the group that did not receive CPAP. PaO_2 was not measured in the present study; however, the saturation values registered at regular 10-second intervals showed higher readings in the CPAP group, leading us to conclude that the pressure of the gas in arterial blood was probably higher in those patients.

The frequency of patients in whom saturation remained above 95% was higher in the CPAP group (50% versus 5,9%). A study published in 2019[28] analyzed the same parameter using a nasal cannula with oxygen flow of 5 L/minute introduced following

pre-oxygenation with a facemask with 100% FiO_2. In that prospective, observational study, 360 children from 40 weeks post-conception to eight years of age who were candidates for surgery were submitted to airway manipulation performed by trainees with no experience in tracheal intubation. Airway manipulation was performed until intubation was successful or until peripheral oxygen saturation of 95%. The children were divided into groups according to whether or not the cannula was used. In the apneic oxygenation group, saturation remained above 95% in 91% of the children, greater than that of the control group (57%). These findings are in agreement with the results of the present study.

The time until recovery of SpO_2 level was shorter in the CPAP group; however, there was no statistically significant difference between the groups. This finding is in agreement with the results of a clinical trial that analyzed the same parameter in apneic patients after pre-oxygenation with and without CPAP of 5 cmH_2O when time to recovery was measured as soon as patients reached a minimum saturation of 93%[18]. Nevertheless, the number of patients in whom T2 was evaluated was small (n=49) and sample size calculation did not take this parameter into consideration. Therefore, there may be a type 2 error (in which no difference is found although a difference does in fact exist). This is common with small samples.

One of the limitations of the present study was the failure to record expired oxygen and nitrogen, parameters of the effectiveness of pre-oxygenation. The amount of CO_2 expired in the return of pulmonary ventilation was not recorded, and this would be

recommendable due to the probable increase in arterial pressure of this gas associated with the already established greater CO_2 production in children. It is a strongpoint that none of the 72 children experienced any significant adverse events such as desaturation, cyanosis or cardiovascular problems.

Finally, considering that most studies on pre-oxygenation use fractions of inspired oxygen of 1; that this strategy, although confirmed to be effective, increases the incidence of atelectasis; that one of the strategies for the prevention of absorption atelectasis is to reduce the fraction of inspired oxygen to 0.8 and that in this study a FiO_2 of 0.60 was used, the use of fractions as high as but no higher than 0.8 should be used together with CPAP in future studies aimed at increasing safe apnea time.

In conclusion, CPAP during induction of anesthesia was effective in increasing safe apnea time in children submitted to general anesthesia for elective surgery. Repeated measures saturation values were higher in the CPAP group and SpO_2 levels remained above 95% in a greater number of patients in this group. There was no evidence of any statistically significant difference between the groups with respect to the time required for saturation to return to pre-apnea levels. Survival analysis showed that survival for a fall in SpO_2 to 95% was greater in the intervention group compared to the control group.

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Table 1. Characteristics of the sample

	Group		p-value
	CPAP (n=34)	**Control (n=34)**	
Sex (%)			
Female	6 (17.7)	10 (29.4)	0.2530*
Male	28 (82.3)	24 (70.6)	
Age (years)	4.34 ± 1.44	4.23 ± 1.51	0.7533
Weight (kg)	18.28 ± 4.87	17.77 ± 4.58	0.6641
ASA (%)			
I	31 (91.2)	33 (97)	0.614†
II	3 (8.8)	1 (3)	
Type of surgery (%)			
Urological surgery	15 (44.1)	11 (32.3)	NC
Herniorrhaphy	12 (35.3)	15 (44.1)	
Combined surgery	3 (8.8)	3 (8.8)	
Intraperitoneal surgery	2 (5.9)	1 (2.9)	
Soft tissue tumor	2 (5.9)	4 (11.9)	

Values are described as means ± SD (continuous variables) and number of patients (categorical variables). Differences between the groups were verified using Student's t-test for continuous variables and Pearson's chi-square test (*) or Fisher's exact test (†) for the categorical variables. ASA: American Society of Anesthesiology; NC: not calculated.

Table 2: Comparison of the main outcomes in the two groups

	Group		RR (95%CI)	p-value
	CPAP	**Control**		
T1, seconds	227.65 ± 84.74	133.68 ± 70.39	-	0.0001
T2, seconds	38.65 ± 49.07	43.12 ± 60.64	-	0.7945
T3, seconds	161.17 ± 61.91	123.28 ± 58.12	-	0.0380
Drop in SpO_2 to 95%, n (%)				
Yes	17 (50)	32 (94.1)	0.5313 (0.3757-0.7512)	0.000
No	17 (50)	2 (5.9)		

Values are described as means ± SD (continuous variables) and number of patients (categorical variables). Differences between the groups were verified using Student's t-test for continuous variables and Fisher's exact test for the categorical variables. RR: relative risk. T1: time between the beginning of apnea and fall in SpO_2 to 95% in all patients (n=68); T2: time of recovery of pre-apnea SpO_2 levels (n=49); T3: time between the beginning of apnea and SpO_2 of 95% in the patients who experienced a fall in SpO_2 (n=49), frequency of fall in SpO_2 to 95% in the two groups (n=68); SpO_2: peripheral oxygen saturation.

Figure 1.

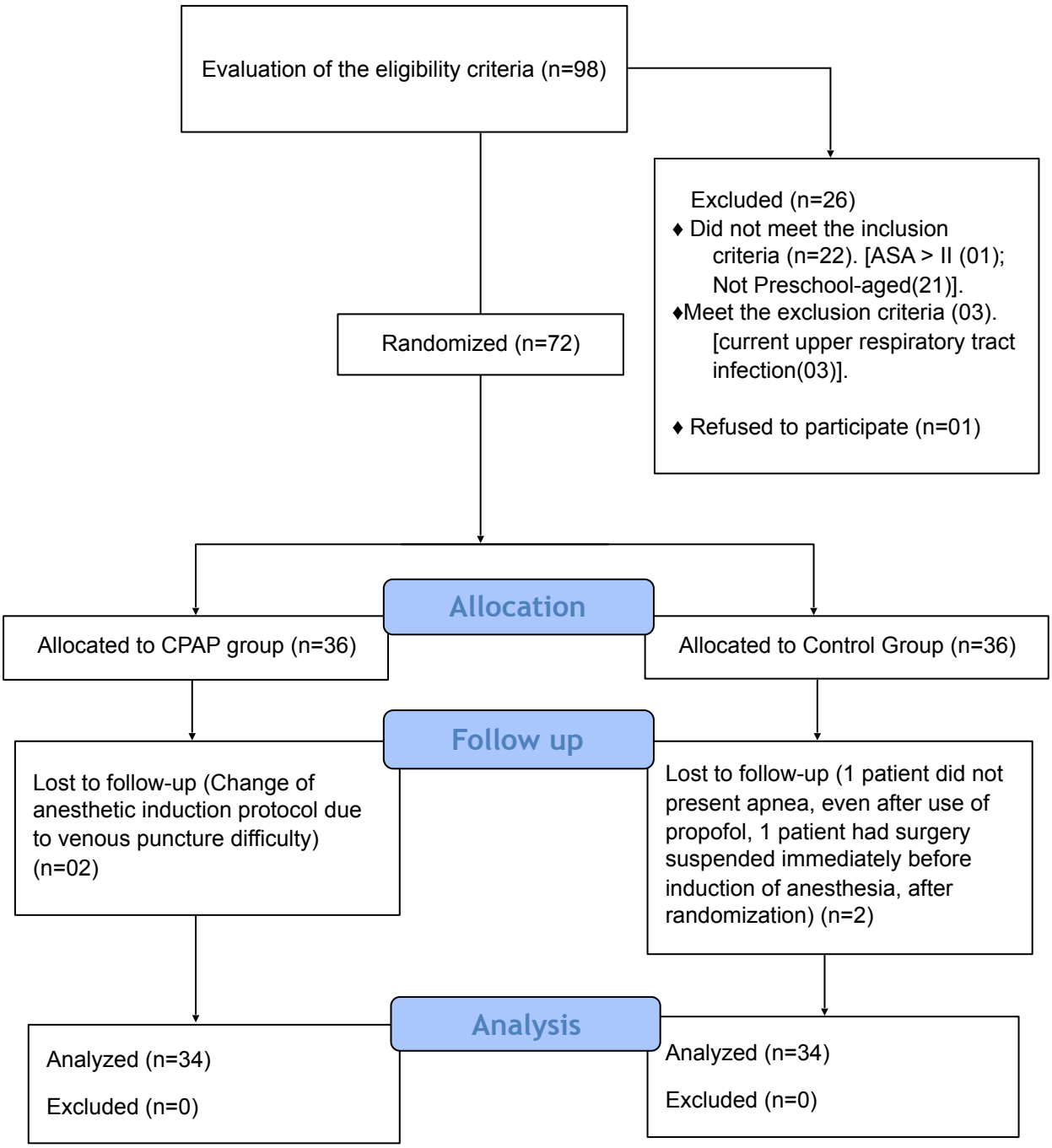

Evaluation of the eligibility criteria (n=98)
Excluded (n=26)
♦ Did not meet the inclusion criteria (n=22). [ASA > II (01); Not Preschool-aged(21)].
♦Meet the exclusion criteria (03). [current upper respiratory tract infection(03)].
♦ Refused to participate (n=01)
Randomized (n=72)
Allocation
Allocated to CPAP group (n=36)
Allocated to Control Group (n=36)
Follow up
Lost to follow-up (Change of anesthetic induction protocol due to venous puncture difficulty) (n=02)
Lost to follow-up (1 patient did not present apnea, even after use of propofol, 1 patient had surgery suspended immediately before induction of anesthesia, after randomization) (n=2)
Analysis
Analyzed (n=34)
Excluded (n=0)
Analyzed (n=34)
Excluded (n=0)

Figure 2.

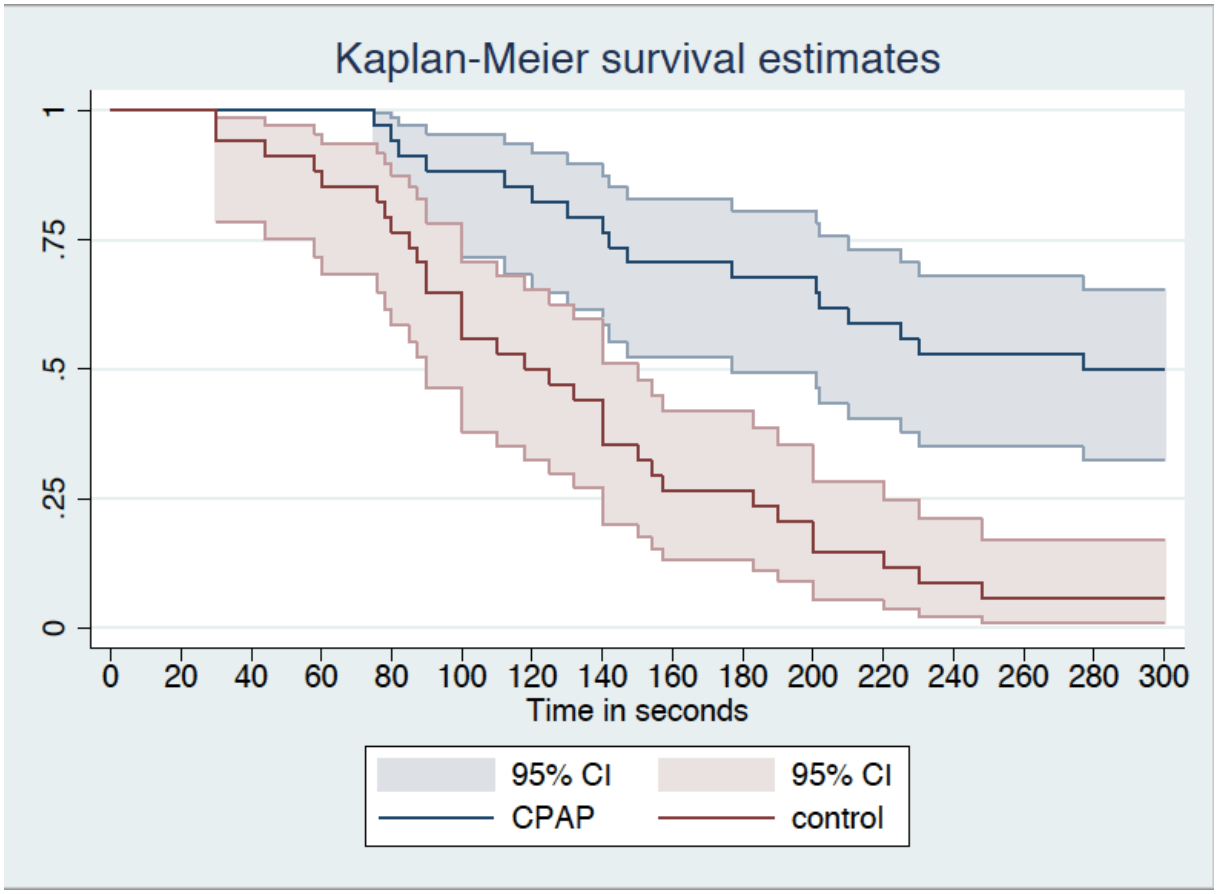
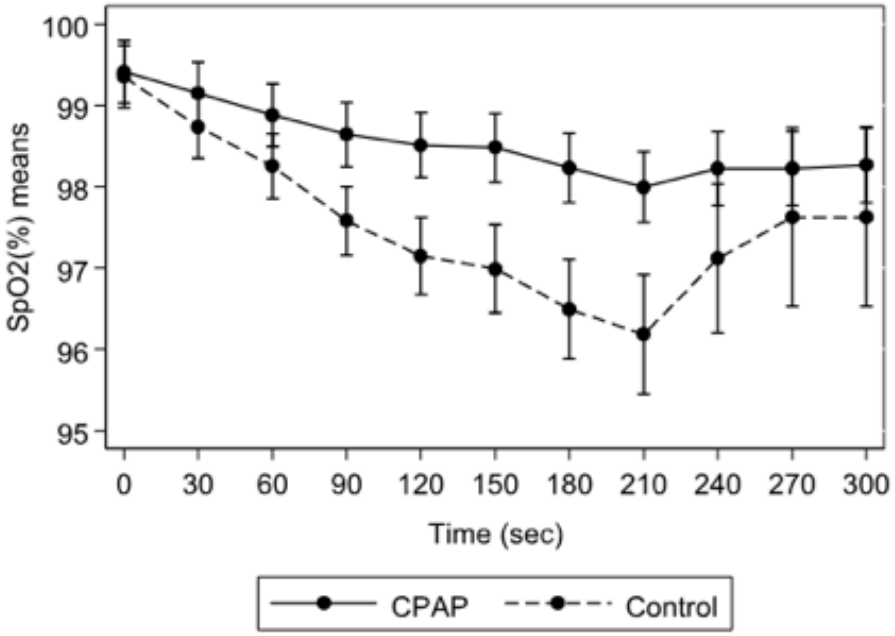

Kaplan-Meier survival estimates
0
.25
.5
.75
1
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
Time in seconds
95% CI
95% CI
CPAP
control

Figure 3.



Time	CPAP Mean ± SD	Control Mean ± SD	Mean difference (CPAP – Control)	*p*
0	99.4 ± 0.20	99.4 ± 0.20	0.1(-0.49 a 0.60)	0.832
30	99.1 ± 0.20	98.7 ± 0.20	0.4(-0.13 a 0.96)	0.138
60	98.9 ± 0.20	98.3 ± 0.20	0.6(0.08 a 1.18)	0.026
90	98.6 ± 0.20	97.6 ± 0.22	1.1(0.48 a 1.64)	<0.001
120	98.5 ± 0.20	97.1 ± 0.24	1.4(0.74 a 1.98)	<0.001
150	98.5 ± 0.21	97.0 ± 0.28	1.5(0.81 a 2.17)	<0.001
180	98.2 ± 0.22	96.5 ± 0.31	1.7(0.99 a 2.48)	<0.001
210	98.0 ± 0.22	96.2 ± 0.37	1.8(0.96 a 2.66)	<0.001
240	98.2 ± 0.23	97.1 ± 0.47	1.1(0.09 a 2.13)	0.034
270	98.2 ± 0.23	97.6 ± 0.56	0.6(-0.59 a 1.79)	0.323
300	98.3 ± 0.24	97.6 ± 0.56	0.6(-0.55 a 1.84)	0.292

Figure Legends

Figure 1. CONSORT flowchart of the patients in the study.

Figure 2. Time until fall in SpO_2 to 95% showing a significant difference between the survival curves (log-rank test; p=0.000).

Figure 3. Mean SpO_2 values every 30 seconds and their respective confidence intervals in the two-group interaction (p=0.0004 for the interaction between the curves).

SD: standard deviation; p-value: Wald test.

VI. CONCLUSÕES

Pressão Positiva Contínua na Via Aérea durante a indução anestésica foi efetiva em aumentar o tempo de apneia seguro em crianças submetidas a anestesia geral para cirurgia eletiva.

Os valores de saturação em medidas repetidas foram superiores no grupo CPAP e uma frequência maior de pacientes nesse grupo não apresentou queda da SpO2 a 95%.

Não houve evidência de diferença significativa entre os grupos quanto ao tempo de recuperação da saturação a valores pré-apneia.

A análise de sobrevida mostrou que a sobrevivência para queda da SpO2 a 95% foi superior no grupo de intervenção em comparação com o grupo controle.

VII. SUGESTÕES E RECOMENDAÇÕES

7.1. RECOMENDAÇÕES PARA A PRÁTICA CLÍNICA

Devido a aumento do tempo de apneia seguro e aos valores superiores de saturação de oxigênio nos pacientes expostos ao CPAP aqui demonstrados, além de considerar que esses parâmetros durante a indução anestésica de crianças potencialmente podem prevenir a ocorrência de complicações graves como parada cardíaca e lesão neurológica, recomendamos a utilização de CPAP para pré-oxigenação de crianças em idade pré-escolar durante a indução de anestesia geral para cirurgias eletivas.

7.2. RECOMENDAÇÕES PARA A PESQUISA

Nosso estudo utilizou CPAP com pressão de 10cmH_2O. Estudos em adultos fizeram uso de pressões que variaram de 5-20cmH_2O. Além disso, os estudos sobre pré-oxigenação utilizam frações inspiradas de oxigênio iguais a um com vistas a aumentar a oferta alveolar desse gás. Essa estratégia, apesar de ser comprovadamente efetiva, aumenta a incidência de atelectasia. Dentre as estratégias para prevenção da atelectasia por absorção está a redução da fração inspirada de oxigênio a 0.8. Nesse estudo, foi utilizada uma FiO_2 de 0.605. Outros parâmetros foram analisados na literatura tais como pressão arterial de gás carbônico ($PaCO_2$) e qualidade da pré-oxigenação através do registro do oxigênio e nitrogênio expirados. Podemos recomendar, portanto, para pesquisas futuras a utilização de diferentes pressões de CPAP associadas a diferentes FiO_2 com o registro do oxigênio, nitrogênio e CO_2 expirados, $PaCO_2$, além do controle do tempo de exposição dos pacientes às diferentes técnicas de pré-oxigenação.

VIII. REFERÊNCIAS

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APÊNDICES

APÊNDICE 1 - LISTA DE CHECAGEM

DATA

Nome: …….

CRITÉRIOS DE INCLUSÃO

	Sim	Não
ASA I ou II		
Crianças em idade pré-escolar		
Crianças submetidas a anestesia geral para cirurgia pediátrica eletiva		

CRITÉRIOS DE EXCLUSÃO

	Sim	Não
Doença pulmonar parenquimatosa pré-existente		
Crianças cianóticas ou com saturação da oxihemoglobina menor que 95% antes da indução anestésica		
História recente (<4 semanas) ou vigência de infecção do trato respiratório superior		

Elegível: Sim ( ) Não ( )

Responsável assinou termo de consentimento livre e esclarecido: Sim ( ) Não ( )

APÊNDICE 2 - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Instituto de Medicina Integral Prof. Fernando Figueira/Escola de Pós-graduação em Saúde Materno Infantil

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Solicitamos a sua autorização para convidar o (a) seu/sua filho (a)_____ {ou menor que está sob sua responsabilidade} para participar, como voluntário (a), da pesquisa PRESSÃO POSITIVA CONTÍNUA NAS VIAS AÉREAS DURANTE A INDUÇÃO DE ANESTESIA GERAL PARA CIRURGIA PEDIÁTRICA ELETIVA: ENSAIO CLÍNICO RANDOMIZADO. Para que você possa decidir se quer ou não participar, precisa conhecer os benefícios, riscos e consequências da sua participação.

Este documento é chamado de Termo de Consentimento Livre e Esclarecido (TCLE) e tem esse nome pois você só deve participar da pesquisa depois de ter lido e entendido essa declaração. Leia as informações com atenção e converse com o pesquisador responsável e equipe da pesquisa sobre quaisquer dúvidas que você tenha. Caso haja uma palavra ou termo que você não entenda, converse com a pessoa responsável por obter esse consentimento, para maiores esclarecimentos. Caso prefira, converse com seus familiares, amigos e equipe médica antes de tomar uma decisão. Após receber todas as informações, você poderá fornecer seu consentimento, rubricando e/ou assinando as duas vias, uma do pesquisador responsável e outra do participante da pesquisa.

Caso não concorde, não haverá penalização nem para o (a) Sr.(a) nem para a criança que está sob sua responsabilidade, bem como será possível ao/a Sr. (a) retirar o

consentimento a qualquer momento, também sem nenhuma penalidade.

Trata-se de uma pesquisa, que é da responsabilidade do pesquisador Jayme Marques dos Santos Neto, que é anestesista e esta estudando uma técnica para ajudar na respiração das crianças durante a cirurgia. O endereço do pesquisador é : Avenida Boa Viagem, 306 apto. 701, Pina, Recife-PE CEP 51011-000; telefone (81)996212977. Dr. Jayme está fazendo a dissertação de Mestrado e esta sendo orientado pela também Anestesista Dra. Flávia Augusta de Orange Lins da Fonseca e Silva, Telefone 81994197979, e-mail orangeflavia@gmail.com

INFORMAÇÕES SOBRE A PESQUISA:

Sua criança está sendo convidada a ser participante de uma pesquisa que estudará o efeito de uma técnica para ajudar na respiração durante o início da anestesia. Chamamos esta técnica de pressão positiva contínua (CPAP).

Para a criança ser operada, ela precisa receber anestesia geral. Para isso, ela respira usando uma máscara de silicone ou plástico que está conectada ao aparelho de anestesia. O gás que vem do aparelho que faz anestesia contém o remédio que faz a criança dormir. Essa técnica é conhecida popularmente como “cheirinho”, mas na verdade é Anestesia Geral, e é usada de forma corriqueira em praticamente todas as anestesias em crianças. O CPAP é feito dessa mesma maneira. A única diferença para a ventilação habitual é que no CPAP o aparelho de anestesia fornece uma pressão que pode ajudar (é o que queremos descobrir) a respirar melhor.

Serão formados dois grupos em que num deles as crianças receberão o CPAP e no outro as crianças receberão a ventilação habitual. Não sabemos em qual grupo sua criança ficará. A participação dela não é obrigatória. O objetivo deste projeto é saber se

o CPAP no início da anestesia melhora a segurança da criança e se o oxigênio no sangue dela permanece em níveis normais por mais tempo.

A participação da sua criança termina tão logo ela volte a condição inicial no estudo quando a sua cirurgia será então realizada. Queremos deixar claro não se tratar de método novo, que já vem sendo utilizado, sendo considerada técnica segura. Em estudos anteriores, não foram verificados efeitos colaterais ou complicações.

Espera-se que, como resultado deste estudo, possa ser estimulado cada vez mais o uso de CPAP no início da anestesia, melhorando a qualidade da assistência na anestesia. Toda a anestesia terá a participação do médico anestesiologista responsável pela cirurgia além do pesquisador que estará presente durante todo o período do estudo, aumentando assim a vigilância sobre os procedimentos realizados na sua criança.

Efeitos indesejáveis são possíveis de ocorrer em qualquer estudo de pesquisa, tais como constrangimento ao assinar este termo, apesar de todos os cuidados possíveis, e podem acontecer sem que a culpa seja sua ou dos pesquisadores. Se sua criança sofrer efeitos indesejáveis como dano associado da sua participação neste estudo, a assistência imediata e integral profissional será providenciada.

As possíveis vantagens para sua criança são maior quantidade de oxigênio no sangue dela, menor chance de problemas no começo da anestesia, aumento do tempo de segurança para ela caso algum problema aconteça também no começo da anestesia e recuperação mais rápida se ela parar de respirar.

As informações desta pesquisa serão confidenciais e serão divulgadas apenas em eventos ou publicações científicas, não havendo identificação dos voluntários, a não ser entre os responsáveis pelo estudo, sendo assegurado o sigilo sobre a participação do/a

voluntário (a). Os dados coletados nesta pesquisa, através de formulários, ficarão armazenados em pastas de arquivo, sob a responsabilidade do pesquisador, no endereço acima informado, pelo período mínimo de 5 anos.

O (A) senhor(a) não pagará nada e nem receberá nenhum pagamento para ele/ela participar desta pesquisa, pois deve ser de forma voluntária, mas fica também garantida a indenização em casos de danos, comprovadamente decorrentes da participação dele/a na pesquisa, conforme decisão judicial ou extra-judicial. Se houver necessidade, as despesas para a participação serão assumidas pelos pesquisadores (ressarcimento com transporte e alimentação).

Em caso de dúvidas relacionadas aos aspectos éticos deste estudo, você poderá consultar o Comitê de Ética em Pesquisa Envolvendo Seres Humanos do IMIP no endereço: **Rua dos Coelhos, nº 300, Boa Vista. Diretoria de Pesquisa do IMIP, Prédio Administrativo Orlando Onofre, 1º Andar tel: 2122-4756 – Email: comitedeetica@imip.org.br**. O CEP/IMIP funciona de 2ª a 6ª feira, das 07:00 às 11:30h (manhã) e das 13:30 às 16:00h (tarde).

_____

Assinatura do pesquisador (a)

CONSENTIMENTO DO RESPONSÁVEL PARA A PARTICIPAÇÃO DO/A VOLUNTÁRIO

Eu, _____, CPF_____, abaixo assinado, responsável por _____, autorizo a sua participação no estudo PRESSÃO POSITIVA CONTÍNUA NAS VIA AÉREAS

DURANTE A INDUÇÃO DE ANESTESIA GERAL PARA CIRURGIA PEDIÁTRICA ELETIVA: ENSAIO CLÍNICO RANDOMIZADO, como voluntário(a). Fui devidamente informado (a) e esclarecido (a) pelo (a) pesquisador (a) sobre a pesquisa, os procedimentos nela envolvidos, assim como os possíveis riscos e benefícios decorrentes da participação dele (a). Foi-me garantido que posso retirar o meu consentimento a qualquer momento, sem que isto leve a qualquer penalidade ou interrupção de seu acompanhamento/ assistência/tratamento para mim ou para o (a) menor em questão.

Local e data _____

Assinatura do (da) responsável: _____

Presenciamos a solicitação de consentimento, esclarecimentos sobre a pesquisa e aceite do sujeito em participar. 02 testemunhas (não ligadas à equipe de pesquisadores):

Nome:	Nome:
Assinatura:	Assinatura:

APÊNDICE 3 – FORMULÁRIO

FORMULÁRIO Nº

GRUPO:

DATA

Características do paciente

Nome: …….

Data da admissão: / / ; Registro:

Data de nascimento : / / ; ASA: I II

Idade (meses): ; Peso (g): ; Altura (cm): ; Sexo: M ( ) F ( )

Cirurgia:

Valor da oximetria de pulso no início da apneia:

Tempo entre o início da apneia e a queda da saturação da oxihemoglobina a 95% (segundos):

Valores da oximetria de pulso

10”: ; 20”: ; 30”: ; 40”: ; 50”: ; 60”: ; 70”: ; 80”: ; 90”: ; 100”: ; 110”: ; 120”: ; 130”: ; 140”: ; 150”: .

Tempo para recuperação dos níveis da saturação da oxihemoglobina na oximetria de pulso pré-apneia (segundos):

Dessaturação até o tempo máximo de cinco minutos: Sim ( ) Não ( )

Complicações: Laringoespasmo ( ) Hipoxemia ( ) Bradicardia ( ) Parada cardiorrespiratória ( ) Morte ( )

ANEXOS

ANEXO 1 - Carta de aprovação do projeto pelo comitê de ética em Pesquisa em Seres Humanos - CEP

INSTITUTO DE MEDICINA INTEGRAL PROFESSOR FERNANDO FIGUEIRA -

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: PRESSÃO POSITIVA CONTÍNUA NAS VIAS AÉREAS DURANTE A INDUÇÃO DE ANESTESIA GERAL PARA CIRURGIA PEDIÁTRICA ELETIVA: ENSAIO CLÍNICO RANDOMIZADO

Pesquisador: Flávia Augusta de Orange

Área Temática:

Versão: 2

CAAE: 79591417.0.0000.5201

Instituição Proponente: Instituto de Medicina Integral Professor Fernando Figueira - IMIP/PE

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.457.340

Apresentação do Projeto:

Ensaio clínico, fase III, paralelo, randomizado a ser desenvolvido no hospital das Clínicas de Pernambuco.Os pacientes (72) serão divididos em dois grupos (36 em cada) nos quais todos ventilarão espontaneamente: o grupo C receberá CPAP e o grupo A utilizará o sistema aberto. Serão incluídas crianças em idade pré-escolar com estado físico, segundo a sociedade americana de anestesia, I ou II e que sejam candidatas a cirurgia eletiva sob anestesia geral. Os critérios de exclusão serão doença pulmonar parenquimatosa pré-existente, crianças cianóticas ou com saturação da oxihemoglobina menor que 95% antes da indução anestésica e história recente (<4 semanas) ou vigência de infecção do trato respiratório superior. A análise estatística descritiva será realizada através de medidas de tendência central e de dispersão para as variáveis quantitativas e através distribuição de frequências para as variáveis qualitativas. Hipótese: O uso de CPAP na ventilação pulmonar de pré-escolares durante a indução de anestesia geral para cirurgia pediátrica eletiva retarda a ocorrência de dessaturação da oxihemoglobina durante período de apneia.

Projeto de Mestrado em Saúde Integral- IMIP

Orientador: Flávia Orange

Coorientador: Lívia Andrade

Endereço: Rua dos Coelhos, 300
Bairro: Boa Vista **CEP:** 50.070-550
UF: PE **Município:** RECIFE
Telefone: (81)2122-4756 **Fax:** (81)2122-4782 **E-mail:** comitedeetica@imip.org.br

Objetivo da Pesquisa:

Avaliar a efetividade do CPAP durante a indução anestésica em aumentar o tempo de apneia até que a saturação da hemoglobina caia a 95% em crianças submetidas a anestesia geral para cirurgia eletiva.

Avaliação dos Riscos e Benefícios:

Adequados.

Comentários e Considerações sobre a Pesquisa:

Projeto viável, oportuno e importante para a população estudada.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Não há.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_978030.pdf	16/12/2017 14:19:58		Aceito
Recurso Anexado pelo Pesquisador	Encaminhamento.doc	16/12/2017 14:12:41	Flávia Augusta de Orange	Aceito
Outros	carta.jpg	04/11/2017 19:38:38	Jayme Marques dos Santos Neto	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	28/10/2017 13:03:20	Flávia Augusta de Orange	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	28/10/2017 12:57:58	Flávia Augusta de Orange	Aceito
Orçamento	Orcamento.docx	28/10/2017 12:41:46	Flávia Augusta de Orange	Aceito
Cronograma	Cronograma.docx	28/10/2017 12:27:52	Flávia Augusta de Orange	Aceito
Folha de Rosto	folhajaime.pdf	14/09/2017	Flávia Augusta de	Aceito

Folha de Rosto	folhajaime.pdf	12:06:25	Orange	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RECIFE, 27 de Dezembro de 2017

Assinado por:
Gláucia Virgínia de Queiroz Lins Guerra
(Coordenador)

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ANEXO 2 - Instruções aos autores

As instruções aos autores da revista *Anesthesiology* encontram-se em http://anesthesiology.pubs.asahq.org/DocumentLibrary/ALN%20IFA_October2018.pdf

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc. • anesthesiology.org

Submission Requirements

Instructions for Authors

Before submitting a manuscript to ANESTHESIOLOGY, please read these Instructions carefully. Each author on a manuscript submission is required to understand the material below.

Manuscripts may only be submitted electronically via the Journal's online submission system: www.editorialmanager.com/aln. Receipt will be acknowledged by e-mail.

For problems with submissions or if you have any questions, please contact the Editorial Office at editorial-office@anesthesiology.org.

Authors Should Allow Approximately 26 days for a Decision.

Authors will be notified if delays occur. Editorial decisions on submissions are final. ANESTHESIOLOGY does not allow rejected manuscripts to be resubmitted.

ANESTHESIOLOGY Uses Crosscheck Plagiarism Detection Software.

Authors are responsible for obtaining and uploading any needed permissions and for clearly and completely identifying any overlapping material and/or quoted or paraphrased passages with proper attribution in the text to avoid plagiarism (including self-plagiarism).

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General Editorial, Legal and Ethical Issues

A. Authorship

Anesthesiology follows the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals to define the criteria required for authorship. All authors must have made substantial intellectual contributions, including: a) participating in the design, execution, analysis, and/or interpretation of the work, b) drafting or revising the manuscript critically for important intellectual content, c) giving final approval of the version to be published, and d) taking accountability for all aspects of the work, including accuracy and validity of the contents, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved All authors should meet all four criteria, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be listed in the Acknowledgments section. Furthermore, the ICJME recommends that each author should be able to identify the specific contributions of their co-authors. The list of persons who qualify as authors and the order listed must be established at the time of original submission. (Any change to authorship after submission is highly discouraged; however, if needed, see section Changes to authorship after submission.)

Authors may indicate two authors in the byline who contributed equally ("#" next to their names and "# These authors contributed equally to the work" at the end of the Title Page). Please note, however, that this will not change how the authors appear in future citations to the article. Manuscripts are received with the understanding that they have been written by the authors; ghostwritten papers are unacceptable (see Cullen D: Ghostwriting in scientific anesthesia journals. *Anesthesiology* 1997; 87: 195-6). Guest authorship and gift authorship are similarly unacceptable (see Rennie D, Flanagin A: Authorship! authorship! guests, ghosts, grafters, and the two-sided coin [editorial]. *JAMA* 1994;271:469-71).

B. Role of the Corresponding Author

Anesthesiology takes very seriously the responsible conduct of research. Each manuscript must have a single Corresponding Author who is accountable for the research and the reporting. The Corresponding Author is the one individual who takes primary responsibility for communication with Anesthesiology during the manuscript submission, peer review, and publication process, and ensures that all the journal's policies and administrative requirements, such as providing details (if requested) of authorship (including that all authors meet all criteria for authorship, and all who meet the criteria should be identified as authors), ethics committee approval, clinical trial registration documentation, and the gathering conflict of interest forms and statements, are met and properly completed. Upon submission, the Corresponding Author is required to attest to the validity and legitimacy of the data and interpretation, on behalf of all authors (who are also responsible for the validity and legitimacy of the data and interpretation). The Corresponding Author is responsible for ensuring that all authors meet the criteria for authorship, have reviewed and approved the manuscript and have completed the conflict of interest disclosures. If the manuscript is accepted, the same corresponding author is the primary contact during the production, publication, and post-publication stages, including reviewing and approving the proof and for all other publication matters. The Corresponding Author must also be available after publication to respond to critiques of the work and to cooperate with any requests from the journal for data or additional information should questions about the manuscript arise after publication. This latter responsibility is an enduring one, as questions may arise years after the submission and publication of a manuscript. The Corresponding Author should have sufficient and ongoing accountability and availability for the research and publication. Each manuscript must have one and only one designated Corresponding Author. The manuscript will be returned without assessment if more than one author is designated as the corresponding author. The role of the Corresponding Author is one of scholarly integrity, in which the Corresponding Author makes a number of statutory and ethical statements on behalf of all authors. Although there are certain administrative roles of the Corresponding Author, these cannot be separated from the other responsibilities, or delegated. Each manuscript should also have the same Corresponding Author throughout the submission, publication, and post-publication process. The designated corresponding author must be the person who signs the cover letter and all communications for all iterations and all phases of the manuscript.

C. Group Authorship

When authorship is attributed to a group in the byline, all members of the group must meet the full criteria for authorship as described above. All members of the group authors must be entered into Editorial Manager to verify their authorship and complete the Copyright Transfer/Disclosure Form when requested. Manuscripts may be held until all authors have verified authorship and confirmed that they have seen the submitted manuscript.

Group authorship requires the same level of participation as principal authorship. Anyone listed as an author must meet all four criteria for authorship, and all others are to be listed as collaborators. An explicit statement as to the exact nature of each author's participation must be provided; upload this under the submission item Authorship Information. Non-authors members of the Group should be listed as Collaborators in the Acknowledgment section. It is important to separately identify Group authors and non-author

collaborators. While there is no limit on the number of authors listed in the byline for an original investigation (provided each author meets all authorship criteria), a long author list may not fit in the space for the author byline. In this case, other options include:

- A Research Group name only in the byline and a list of the individual group authors in the article Acknowledgment section along with their affiliations, contributions, and conflicts of interest disclosures. In PubMed, the Group name is listed and all authors are listed in the order they appear in the Acknowledgment section.
- Some named authors in the byline, in combination with a Research group. Since all members of the Research Group must be qualified authors, and all meet authorship criteria, the byline is Individual Authors A, B, C, etc "and" a Research Group. All members of the Research Group are authors as designated by "and" the Research Group byline. The name of the Research Group and the byline authors and the non-byline authors in the Group are listed in the Acknowledgment section at the end of the article, along with their affiliations, contributions, and conflicts of interest disclosures. Non-author members of the Research Group may be designated as Collaborators and listed in the Acknowledgments section of the article. In PubMed, the authors named in the byline and the individual non-byline authors in the Research Group are listed as authors along with the Group Name.

D. Group Collaborators

Those members of a group that do not meet all of the criteria for authorship may be listed as collaborators provided that they substantially contributed to the work reported in the manuscript. These members will be listed as collaborators in PubMed and in the published article. Collaborator names and degrees should be listed in an appendix. The corresponding author is responsible for completing the acknowledgement statement for the manuscript and only including those members of the group who have substantially contributed and have provided written permission to be listed in the published article. Group members listed as collaborators will not be required to complete the Copyright Transfer/Disclosure form.

For an example of how group collaborators appear in PubMed, see https://www.ncbi.nlm.nih.gov/pubmed/26872366

If relevant to your submission, contact the Editorial Office at editorial-office@anesthesiology.org for further information about how to distinguish and mark group authorship and group collaborators.

E. Changes to authorship after submission

Authors on a work must be established before submission, and all authors must meet all the criteria for authorship (see I.A). Any change in authorship (order, addition, removal, designated corresponding author) after the original submission is considered unusual and is *highly discouraged*. A request for such a change must be made in writing by the corresponding author, requires a clear and thorough explanation and justification for the change, and must be approved by the Editor-in-Chief.

In addition to the request from the corresponding author, each author, including, as relevant, the person being added or removed, must independently provide signed, written approval of the change to be submitted to *Anesthesiology*. This documentation must also include a definition of the contribution of every person listed as an author on the initial submission and the subsequent version/s. Each person must explain their contribution to the original manuscript and revised manuscript/s and their understanding of the contributions of each other person listed as an author to the original manuscript and revised manuscript/s. You may wish to contact the Editorial Office for the full procedure and required documentation.

The submission will be returned to the authors until all appropriate information is received. The corresponding author is responsible for collating all the documentation and submitting it under the submission item Authorship Information when returning the manuscript into the online system. While the Editor-in-Chief considers the request, further processing of the manuscript will be suspended. Requests for change in authorship are not guaranteed and are granted at the discretion of the Editor-in-Chief.

Any changes (author order, addition, removal) to authors listed in a Research Group or as Group Collaborators made after manuscript submission must be requested by the corresponding author and require a clear and thorough explanation and justification for the change, and must be approved by the Editor-in-Chief. The person being added or removed from the Research Group or Group Collaborators, and each author listed on the byline must independently provide signed, written approval of the change to be submitted to *Anesthesiology*. Other members of a Research Group or Group Collaborators, not listed on a byline, do not have to provide such approval. However, the Corresponding Author must provide a written statement to *Anesthesiology* that s/he has informed all co-authors of the change in Research Group or Group Collaborators and the reason for the change and provide a copy of the notice to *Anesthesiology*.

F. Copyright

Each author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, "Uniform

Requirements for Manuscripts Submitted to Biomedical Journals." A copy of the form is made available to the submitting author within the Editorial Manager submission process. Co-authors will automatically receive an email with instructions on completing the form upon revision.

G. Compliance with Funder-mandated Open Access Policies

A number of nonprofit research funding agencies require authors to comply with open access mandates and publish their research under a creative commons license. At submission, please disclose any applicable funding sources that require open access publication. Refer to http://www.wkopenhealth/inst-fund.php, if needed, for a list of Funder-Mandated Open Access Policies which Anesthesiology recognizes. If your nonprofit research funding agency is not on this list, and you have eligibility questions, please contact the Editorial Office. Open access eligibility decisions are made by the Editor-in-Chief.

Note that this is not the same as research funding agencies that require or request authors to submit an accepted manuscript after peer review and acceptance but not the final published article to a repository that is accessible online by all without charge.

Authors of articles that have been funded from sources that require open access publication are required to sign the Open Access License Agreement prior to publication of the applicable article. Under the Open Access License Agreement, authors retain copyright for all articles they opt to publish open access, but grant an exclusive license for the article to be made available under the terms of a Creative Commons user license. The Creative Commons License required by the funding source shall apply.

Authors of articles funded by the agencies listed above who are interested in open access publication should fill out the open access option upon manuscript submission in Editorial Manager and include the name of their funding body. This choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.

The article processing fee is charged on acceptance of the article and should be paid within 30 days by the author, funding agency or institution. Payment must be processed for the article to be published open access. Please contact the Editorial Office to receive the Open Access License Agreement that is to be signed in connection with the open access publication of an article.

H. Duplicate, Prior or Divided Publication

Submitted manuscripts must not have been published elsewhere, in whole or in part, on paper or electronically. This includes personal, departmental, educational or other websites, such as Nature Precedings (precedings.nature.com/). This does not apply to abstracts of scientific meetings, or to lecture handouts (e.g., ASA Annual Meeting), which should be disclosed on the title page.

It is improper for authors to submit a manuscript describing essentially the same research simultaneously to more than one peer-reviewed research journal. To do so is to overuse valuable editorial and reviewing time. It also increases the risk of duplicate publication. *Anesthesiology* discourages authors from dividing the results of a single study into multiple papers. Do not submit several small manuscripts; a single comprehensive paper is preferable. If the authors believe that subdivision is appropriate, or if multiple articles may result from the same study, contact the Editor-in-Chief through the Editorial Office. Authors must clearly disclose at submission if another manuscript derived from the same experiment has been published previously or has been or will be submitted to another journal.

I. Scientific Misconduct

When *Anesthesiology* has concerns or receives allegations of scientific misconduct, *Anesthesiology* reserves the right to proceed according to the procedures described below. *Anesthesiology* recognizes its responsibility to appropriately address concerns of allegations of misconduct. Examples of misconduct include falsification of data, plagiarism, improper designations of authorship, duplicate publication, misappropriation of others' research, failure to disclose conflict(s) of interest, and failure to comply with applicable legislative or regulatory requirements. Misconduct also includes failure to comply with any rules, policies, or procedures implemented by *Anesthesiology*.

Process: In general, *Anesthesiology* follows the recommendations of the Committee on Publication Ethics (COPE) when working to address allegations of misconduct. When a concern or allegation is raised, involved parties generally will be contacted to provide an explanation of the situation. As needed, *Anesthesiology* may also contact the institution at which the study was conducted and any other involved journals. *Anesthesiology* will attempt to determine whether there was misconduct and the Editor-in-Chief will respond with an appropriate action. Examples of action include:

- Sending a letter of explanation only to the person(s) involved or against whom the allegation is made.
- Sending a letter of reprimand to the same person(s), warning of the consequences of future, similar instances.
- Sending a letter to the relevant head of the educational institution and/or financial sponsor of the person(s) involved, expressing the concerns and information collected

- Publishing in *Anesthesiology* a notice of duplicate publication, "salami" publishing, plagiarism, or other misconduct, if clearly documented. In cases of ghost-written manuscripts, the notice may include the names of the responsible companies as well as the submitting author(s).
- Providing specific names to the media and/or government organizations, if contacted regarding the misconduct.
- Formally withdrawing or retracting the article from *Anesthesiology*, and informing readers and indexing authorities.
- Banning an author or authors from publishing any manuscript in *Anesthesiology* for a specified time period, with notice to the author(s)' institution.

J. Human Studies

Human experimentation must conform to ethical standards and be approved by the appropriate Institutional Review Board (IRB). A statement concerning IRB approval and consent procedures must appear at the beginning of the Methods section. Any systematic data gathering effort in patients or volunteers must be approved by an IRB or adhere to appropriate local/national regulations. The Editors of *Anesthesiology* are concerned about appropriate IRB review and informed consent. Authors may be questioned about the details of consent forms or the consent process. On occasion, the Editor-in-Chief may request a copy of the approved IRB application from the author. Lack of appropriate consent or documentation may be grounds for rejection. Local IRB approval does not guarantee acceptability; the final decision will be made by the Editor-in-Chief. A specific example is that of neuraxial or peri-neural administration of drugs because lack of toxicity from systemic administration does not exclude toxicity when injected near these neural structures.

The Editor-in-Chief will consider appropriate study of drugs by these routes to include:

- Drugs approved for intrathecal, epidural, or peri-neural administration by the United States Food and Drug Administration (FDA) or the equivalent regulatory agency for the country in which the study took place.
- Drugs not approved by these routes, but which are widely used (e.g., fentanyl for intrathecal or epidural administration). The publication of dosing guidelines in multiple textbooks represents a reasonable demonstration that a drug is widely used and accepted.
- Study performed under an Investigational New Drug (IND) application approved by the FDA or the equivalent agency in the investigator's country. Investigators in the United States are directed to www.fda.gov/cder/about/smallbiz/clinical_investigator.htm for further information on obtaining an investigator IND.

K. Animal Studies

Experimental work on animals must conform to the guidelines laid out in the Guide for the Care and Use of Laboratory Animals, which is available from the National Academy of Science; a text-only version is available at www.nap.edu/readingroom/books/labrats. Adherence to all relevant regulations and/or approval of the appropriate institutional Animal Care Committee or governmental licensure of the investigator and/or laboratory must be obtained. A statement concerning such approval must be included at the beginning of the Methods section. The Editors of *Anesthesiology* are concerned about appropriate animal care. Authors may be questioned regarding the use of anesthetics, muscle relaxants, and postoperative analgesics. On occasion, the Editor-in-Chief may request a copy of the approved Animal Care Committee application from the author. Major issues are a) the postoperative use of analgesics following surgical procedures and b) the use of neuromuscular blocking drugs, particularly in minimally sedated animals. Local committee approval does not guarantee acceptability; the final decision will be made by the Editor-in-Chief. Investigators are encouraged to read the following Editorial: Drummond JC, Todd MM, Saidman LJ: Use of neuromuscular blocking drugs in scientific investigations involving animal subjects: The benefit of the doubt goes to the animal. *Anesthesiology* 1996; 85: 697-9.

L. Conflicts of Interest and Sponsorship

Conflicts of interest, sponsorship, and other relevant declarations must appear on the title page and be indicated in the system as part of the submission steps. The Editors of *Anesthesiology* are concerned about any real or perceived conflicts of interest. Authors must declare all funding sources supporting their work or its authors, even if support is indirect, e.g., to a local research foundation that funded the project. This includes departmental, hospital, or institutional funds. The authors must disclose commercial associations that might pose a conflict of interest in connection with the work submitted. Consultancies, equity interests, or patent-licensing arrangements should also be noted at submission. For further information, see Todd MM, Saidman LJ: Academic-industrial relationships: The good, the bad, and the ugly. *Anesthesiology* 1997; 87: 197-200.

M. Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request authors to submit the post-print version (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to *Anesthesiology*'s authors, Lippincott Williams & Wilkins will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print version of an article based on research funded in whole or in part by the National Institutes of

Health (NIH), Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The Copyright Transfer Agreement provides the mechanism.

N. Study Design Issues:

1. **Preclinical Trials.** Authors of preclinical trials (experiments in animals, cells, molecules, or other biological foci) should consult ARRIVE guidelines for transparent reporting (Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG: Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol 2010; 8: e1000412). Authors should report 4 specific elements of study design: a) adequate description of the methods used to allow replication; b) whether measures to reduce bias, including random allocation and blinding, were used and if so, how they were performed; c) how the sample size was determined; d) the data analysis plan. For details see the following editorial: Eisenach JC; Warner DS,, Houle TT; Reporting of Preclinical Research in ANESTHESIOLOGY: Transparency and Enforcement. *Anesthesiology* 2016;.doi: 10.1097/ALN.0000000000001044.
2. **Surveys.** *Anesthesiology* welcomes papers based on well done surveys. However, the quality of the survey methodology is often a factor in the Editor-in-Chief's decision. Interested authors should review the material contained in the following editorial: Burmeister LF. Principles of Successful Sample Surveys. *Anesthesiology* 2003; 99: 1251-1252.
3. **Observational Studies.** Authors of observational studies should consult the guidelines published by the STROBE group. As a clarification of this guideline, we require transparent reporting of whether a statistical plan was defined prior to accessing data, and, if so, the details of that plan. (Eisenach JC, Khetherpal S, Houle TT.; Reporting of Observational Research in Anesthesiology: The Importance of the Analysis Plan. *Anesthesiology* 2016; doi: 10.1097/ALN.0000000000001072)
4. **Clinical Trials:** Authors of clinical trials (regardless of size) should consult the guidelines published by the CONSORT group [Moher D, et al for the CONSORT Group: The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285:1987-91 at http://www.consort-statement.org/] and the following editorial: Todd MM: Clinical research manuscripts in Anesthesiology. *Anesthesiology* 2001; 95: 1051-1053. Authors should consult the CONSORT checklist for items required when reporting a randomized clinical trial.

   Registration of Clinical Trials: All clinical trials involving assignment of patients to treatment groups must be registered before patient enrollment, effective with trials beginning May 1, 2013. For trials that began enrollment before May 1, 2013, registration is strongly recommended and if the trial reported was not registered, please comment on this matter on the title page. The registry, registration number, principal investigator's name, and registration date must be stated in the first paragraph of the Methods section of the manuscript. It must also be included on the title page of the manuscript.
   A number of registries have been approved by the International Committee of Medical Journal Editors (www.icmje.org/faq_clinical.html), including www.clinicaltrials.gov (the most commonly used registry in the United States), isrctn.org, www.umin.ac.jp/ctr/index/htm, www.anzctr.org.au, and www.trialregister.nl. Submissions that have registered with the European Clinical Trials Database, EudraCT (eudract.ema.europa.eu/), meet this requirement.
5. **Systematic reviews, narrative reviews and meta-analyses.** Authors of these article types are encouraged to read the section below on submitting proposal ideas. Authors reporting on a collection of existing literature (a review) should distinguish between a systematic review (some article inclusion criteria established and all relevant articles were included in the review) and a narrative review (authors picked up a representative collection of articles to include). Authors writing systematic reviews and meta-analyses should review the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements and guidelines. It is required that such submissions to Anesthesiology be accompanied by the PRISMA Checklist. Where appropriate, such submissions must employ the GRADE criteria for grading quality of evidence and strength of recommendations.

O. Editorial Decisions and Appeals Process

Decisions on submissions to this journal are final. *Anesthesiology* does not allow rejected manuscripts to be resubmitted as new manuscripts; resubmissions of rejected submissions will be returned without assessment. If an author wishes to appeal an editorial decision, the appeal must be based on evidence, provided by the corresponding author, that the reviewers have misunderstood the scientific content of the manuscript, that there is evidence of reviewer conflict-of-interest or bias, and/or that there are demonstrably incorrect statements of fact in the reviews. There are two phases to the appeals process; contact the Editorial Office for complete information if you wish to submit a formal appeal. Decisions whether to consider or accept an appeal are ultimately made by the Editor-in-Chief. Informal comments or complaints after decision that do not follow the appeals process will not be considered.

P. Presubmission Reviews and Proposals

The journal editors do not provide pre-submission reviews. However, if you wish to submit a manuscript for consideration as a Narrative Review, Systematic Review, Meta-Analysis, Special Article, or Clinical Focus Review, please e-mail a proposal to the Editorial Office that includes 1) the proposed article type, 2) a 250-word summary and outline of the proposed manuscript, 3) a list of the authors and their qualifications. For Narrative Reviews, Systematic Reviews or Meta-Analysis, please identify the PMID of the three most recent reviews on the topic (if existing) and identify objective difference(s) from these in the proposed review. Do not send complete manuscripts. NOTE: The person who e-mails the proposal is to be the same person who will be the designated corresponding author if the proposal is approved for submission; see Role of the Corresponding Author.

Types of Papers

A. **Original Investigations**
The Original Investigation article type consists of the four central aspects of the medical specialty of anesthesiology:

- Perioperative Medicine
- Critical Care Medicine
- Pain Medicine
- Education

Although there is overlap, authors will choose one of these areas as the article type during the submission process. Original Investigation submissions range in length from 1,500 to 4,000 words. Abbreviated Titles and structured Abstracts are required (see the section on Manuscript Preparation).

B. **Images in Anesthesiology**
Images in Anesthesiology (IiA) are succinct submissions that couple an interesting, novel, or highly educational image with brief text designed to highlight the pertinent anesthesiology-focused information displayed by the image. Supplemental video content can be included to expand the visual learning. The focus of an IiA submission is the image itself, and key educational points raised in the body of the text should be directly related to observation of the image. The IiA section of the Journal is **not** to be used as a forum for case reports. IiA manuscripts are intended to educate medical students, residents, fellows, anesthesiology practitioners, and interested physicians and scientists.

IiA manuscripts are limited to 250 words, should include 3 references, and must not have more than 4 authors. The image should be one frame that on occasion might have two coupled panels. Labeling of the image should focus attention to the intended educational message. Rather than including a legend for the image, its description should be incorporated into the body of the text.

C. **Mind to Mind**
Mind to Mind is a creative writing section devoted to exploring the abstract realm of our profession and our lives. Submitted works can be poetry, fiction, or creative nonfiction. Limit submissions to 1,200 words or less. Authors can be students or a current or emeritus member of the anesthesia, perioperative, critical care, or pain teams. Patients may submit writing about their medical experience. Provide a Title Page (See Title Page III.B). The piece may be published anonymously at the author's request, however, authors' names, conflicts of interest, and other information are required during submission on the title page. Pieces must respect confidentiality as needed.

D. **Letters to the Editors**
Letters to the Editor should be brief (250 to 1,000 words). A few references, a small table, or a pertinent illustration may be used. Supply an original title for the Letter on the Title Page. (See Title Page III.B) Do not submit Abbreviated Titles, Summary Statements, and Abstracts. Letters may offer criticism of published material. They must be objective and constructive. Letters to the Editors are not a venue for case reports, and authors must attest during the submission process that a case description is not included in the submission.

NOTE: Letters commenting on published articles must be received in the Editorial Office no later than two months after the first of the month of the original article print publication date.

"Freestanding" Letters to the Editors also may discuss matters of general interest to anesthesiologists, without specific linkage to recently published articles.

E. **Review Articles**
Review Articles are invited or pre-approved comprehensive articles that summarize and synthesize older and current ideas and may suggest new concepts. They may cover broad areas and with appropriate depth. They may be clinical, investigational, or basic science in nature and intended for one or more of these readerships. Reviews should be written by recognized experts in the field, with requisite experience, as evidenced by substantial peer reviewed publications in the topic area. They may range in length from 3,000 to 8,000 words. Review articles are well-served by including summary figures and/or tables that help emphasize critical concepts. An unstructured abstract of 150 words maximum (one- or two-paragraph summary of the key points) is required. An Abbreviated Title and a Summary Statement is required on the Title Page (see the section on Manuscript Preparation III.B). The Abbreviated Title should be limited to 50 characters maximum. The Summary Statement should be limited to 35 words maximum.

Meta-analyses and systematic reviews are not considered Review Articles. These are considered Original Investigations, require a structured abstract (see Abstract section) and should be submitted to the appropriate section (Perioperative Medicine, Critical Care Medicine, or Pain Medicine).

Individuals interested in writing a Review Article should submit a proposal to the Editorial Office before submission to learn whether the article topic would be of interest; include a 250-word synopsis and outline of the intended manuscript with a list of the authors and their qualifications. Do not send the full manuscript. NOTE: The person who e-mails the proposal is to be the same person who will be the designated corresponding author if the proposal is approved for submission; see Role of the Corresponding Author. Contact the Editorial Office at editorial-office@anesthesiology.org.

F. **Clinical Focus Review (prev. Clinical Concepts and Commentary)**

Clinical Focus Review (previously Clinical Concepts and Commentary) (CFR) are brief reviews with commentary (2,000 to 3,000 words) focused on clinical topics that are invited or pre-approved. CFR articles are intended for the practicing clinician, should be written by individuals with experience and expertise in the field, be evidence-based, and emphasize the clinical aspects of the subject. An Abbreviated Title and a Summary Statement is required on the Title Page (see the section on Manuscript Preparation III.B). The Abbreviated Title should be limited to 50 characters maximum. The Summary Statement should be limited to 35 words maximum. Articles should be accompanied by no more than 50 references. This article type has no abstract. If accepted for publication, we seek to include two color illustrations (any combination of tables and/or figures to be determined by the authors) to enhance the effectiveness of the publication. Illustrations submitted with the manuscript can be in draft form. A professional artist may produce the final figures.

Individuals interested in writing a CFR article should submit a proposal to the Editorial Office before submission to determine whether the article topic would be of interest; include a 250-word synopsis and outline of the intended manuscript with a list of the authors and their qualifications. Do not send the full manuscript. NOTE: The person who e-mails the proposal is to be the same person who will be the designated corresponding author if the proposal is approved for submission; see Role of the Corresponding Author.

G. **Special Articles**

Special Articles are invited or pre-approved. *Anesthesiology* occasionally publishes Special Articles (e.g., history, education, demography, contemporary issues, etc.). An unstructured abstract of 150 words maximum (one- or two- paragraph summary of the key points) is required. An Abbreviated Title and a Summary Statement is required on the Title Page (see the section on Manuscript Preparation III.B). The Abbreviated Title should be limited to 50 characters maximum. The Summary Statement should be limited to 35 words maximum.

Individuals interested in writing a Special Article should submit a proposal to the Editorial Office before submission to learn whether the article topic would be of interest; include a 250-word synopsis and outline of the intended manuscript with a list of the authors and their qualifications. Do not send the full manuscript. NOTE: The person who e-mails the proposal is to be the same person who will be the designated corresponding author if the proposal is approved for submission; see Role of the Corresponding Author.

H. **Other Article Types**

Anesthesiology also publishes 1) Editorials, 2) Classic Papers Revisited, and 3) Review of Educational Materials (book reviews). These are typically solicited. Please contact the Editorial Office for further information.

NOTE: Case reports, case series, case scenarios, and correspondence/Letters to the Editors describing cases are not published by *Anesthesiology* and are not accepted for review (see Eisenach JC: Case reports are leaving *Anesthesiology,* but not the specialty. Anesthesiology 2013; 118:479).

Manuscript Preparation

All manuscripts should be submitted via the journal's online submission and review system; do not submit a manuscript via e-mail. Make sure your submission is complete and correct before completing the steps to submit it to the journal office. Manuscripts that do not satisfy minimum submission requirements will be returned to authors to correct. You will have an opportunity to review the constructed PDF file before approving the submission. Review this document carefully; after it is sent to the editors and reviewers, no changes can be made until an editorial decision is reached.

All submissions require a Title Page (See "Title Page" in previous "Manuscript Preparation" Section, item B). Manuscripts must be double-spaced. Fonts should be 10 point or larger. All four margins should be at least 2.5 cm (1 in). If a manuscript is formatted for A4 paper, leave at least a 5 cm (2 in) margin at the bottom of the page. Number pages consecutively, preferably the upper right corners.

At first submission, manuscripts may be submitted as single Word document files, including title page, references, figure legends, figures, and tables. All manuscript components need to be included to allow for evaluation of your manuscript. If the editors request a revision, however, source files of the manuscript, figures, and tables will be required as well as other submission and publication elements.

A. General Arrangement, All Submissions

ALL articles should be arranged in the following order.

1. Cover letter (optional)
2. Manuscript, as a single file in word processing format (eg, .doc), consisting of Title Page, Abstract (if required for the article type; see relevant section), Body Text, References, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file
3. Tables (each Table should be a separate file in word processing file format, eg, .doc)
4. Appendices (each Appendix should be a separate word processing file format, eg, .doc)
5. Figure Legends (placed consecutively, in numerical order, all on the same page)
6. Figures (each Figure should be a separate file in figure file format)
7. Other submission elements (Supplemental Digital Content, etc.)

B. Title Page

All submissions require a Title Page with the following information on the first page(s) of the manuscript file:

1. Article Title (do not use abbreviations in the title);
2. Author Information: First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly
3. Corresponding Author: Name, mailing address, phone number, and e-mail address of the corresponding author; only one corresponding author may be designated for the entirety of the review and publication process; see section I.B);
4. Clinical trial number and registry URL, if applicable;
5. Prior Presentations: Note any presentation/s of the work at conferences for meetings; include name, exact date, location;
6. Acknowledgments: List individuals or organizations to be acknowledged, if any. Provide complete name, degrees, academic rank, department, institutional affiliation, city, state, country, and a brief description of their contribution;
7. Word and Element Counts: Number of words in the Abstract, in the Introduction, and in the Discussion section;, number of Figures; number of Tables; number of Appendices, if any; and number of Supplementary Digital Files, if any. Make sure all intended elements are submitted;
8. Abbreviated Title (Running Head): State the essence of the article (50 characters maximum) for all article types except Images in Anesthesiology, Letters to the Editor, and Mind to Mind;
9. Summary Statement: Brief statement (35 words maximum) to be printed in the Table of Contents for Review Article, Clinical Focus Review, and Special Article submissions;
10. Funding Statement: Disclosure of all financial support for the work, including departmental or institutional funding/support. Comments such as "No Funding Received" are not acceptable. If only institutional/hospital/departmental funds were used, add the following statement: "Support was provided solely from institutional and/or departmental sources." Be sure to specify funding from any of the following organizations: National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute

(HHMI) (see section on Compliance with NIH and Other Research Funding Agency Accessibility Requirements). Provide both the name and location of each funding agency/source.

11. Conflicts of Interest: Any conflicts of interest for any or all authors within the 36 months of submission. If no competing interests, please add the following statement: "The authors declare no competing interests." Refer also to the relevant section.

If any of these elements are not applicable to your submission, write "not applicable" after the number and topic; for example, "5. Prior Presentations: Not applicable."

C. Abstract

Original Investigations (Perioperative Medicine, Critical Care Medicine, Pain Medicine, and Education) require a structured abstract. It should be limited to 300 words. The structured abstract should contain four labeled paragraphs: Background, Methods, Results, and Conclusions. Abstracts may be the only part of an article which is read, and must stand alone from the body of the manuscript. In order to enhance comprehension, the use of nonstandard abbreviations or acronyms in the Abstract is not allowed.

A list of standard abbreviations accepted by the journal may be found at anesthesiology.pubs.asahq.org/DocumentLibrary/08302018_abbreviations.pdf

Review Articles and Special Articles require an unstructured, one- or two-paragraph summary of the key points of the article of 150 words or fewer.

Make sure the text of the Abstract in the manuscript file and in the system match exactly.

D. Body Text

1. Introduction (new page, 500-word limit;
2. Materials and Methods (new page): A subsection entitled "Statistical Analysis" should appear at the end of the Materials and Methods section when appropriate (for comments re. Statistics, see below). Include, as relevant, statements about informed consent, animal care, IRB approval, and/or clinical trial registration;
3. Results (new page);
4. Discussion (new page, 1,500-word limit): The discussion should focus on the findings in the current work.

NOTES

- ABBREVIATIONS: To enhance comprehension, the use of nonstandard abbreviations or acronyms is strongly discouraged. A list of standard abbreviations accepted by the journal may be found at List of Standard Abbreviations. See also L.2.
- CLAIMS OF PRIMACY: Do not make any ordinal/primacy claims, eg, "this is the first study"; "this is the only study"; "we are the first to demonstrate."
- LENGTH: The Introduction and Discussion sections should not exceed 2,000 words combined. It is recommended that the Introduction be no longer than 500 words and the Discussion section no more than 1,500 words. Manuscripts that do not meet these word limits may be sent back to the authors.
- PAGE NUMBERING: Number all pages in the manuscript file.

E. References

Number references (as superscripts) in the sequence they appear in the text. Use abbreviated titles of the medical journals as they appear in Index Medicus (see http://www.nlm.nih.gov/tsd/serials/lji.html). Include only references accessible to all readers. Do not include articles published without peer review or material appearing in programs of meetings or in organizational publications. Sites on the World Wide Web (URLs) may be used as references, provided the citation includes the last accessed date. Abstracts are acceptable as references only if published within the previous 3 years. Manuscripts in preparation or submitted for publication are never acceptable as references. If you cite accepted manuscripts "In Press" as references, please provide one electronic copy (e.g., Word, PDF) when you submit the new manuscript and mark them as "In Press, Reference # ___."

Supply all authors' names for each reference; do not use "et al." Please confirm the accuracy of your references by comparison with original sources, not with someone else's reference lists, and examine your citations for typographical errors. Supply complete publication information for all references.

Anesthesiology style is that references in legends to tables and figures be cited in the order in which they occur (as if they were cited in the text). This includes references that appear only in a table or figure legend and not in the text. Because it is recognized that authors may use software to format references, and to ensure that references are cited in the proper order, references cited in a table or figure legend should also be cited in the text at the first (but not necessarily subsequent) callout to that figure or table; a reference should not be cited only in a table or figure legend. If references are cited only in a table or figure legend, this will require renumbering of references during composition of the manuscript and possibly delay publication.

Use the following reference formats:

1. Journal: Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P: Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: Results of a randomized trial. *Anesthesiology* 2002; 97:540-9
2. Book: Barash PG, Cullen BF, Stoelting RK: Clinical Anesthesia, 3rd edition. Philadelphia, Lippincott-Raven Publishers, 1997, pp 23-4
3. Chapter: Blitt C: Monitoring the anesthetized patient, Clinical Anesthesia, 3rd edition. Edited by Barash PG, Cullen BF, Stoelting RK. Philadelphia, Lippincott-Raven Publishers, 1997, pp 563-85

F. Tables

Number tables consecutively in order of appearance (Table 1, etc.). Make sure tables are cited/called-out in the text in the correct order. Each Table should be submitted as a separate file. Each table must have a title and include footnotes when appropriate. Make sure any symbols and abbreviations used in the tables are defined. Tables must be word processing document format (eg, .doc). Do not submit tables as image files.

G. Appendices

Upload each appendix as a separate file. Number each appendix. Each appendix must be cited within the text, in consecutive order.

H. Figure Legends

Supply a legend/caption for each figure, preferably on the last page of the manuscript file. For review purposes, figures and their accompanying legends can be included as a group at the end of the manuscript file. If a revision is requested, authors will be asked to supply figures as separate original source files with textual legends/captions grouped on a single page in the manuscript file.

I. Figures

Figures should be prepared according to the professional standards of this Journal in appropriate file format with sufficient resolution for publication. If a single figure contains more than one panel, each panel must be identified alphabetically (e.g., A, B, etc.) and should read left to right in presentation. The figures must be cited in the text in the same, consecutive numeric order. Each Figure should be submitted as a separate file, clearly labeled with the figure number (e.g., Figure1.tif, Figure2.eps, etc.). Make sure that any special symbols used in a figure (e.g., asterisk, double asterisk) are explained in the legend/caption.

Format: Acceptable graphics formats are .tif, .eps, .jpg, or .pdf.

Resolution: Photographic or halftone figures should be saved at 300 ppi resolution, with image sizes no smaller than 4 x 6 inches, approximately 1200 to 1800 pixels wide. Line-art, graphs, charts, diagrams must be 1200 ppi, approximately 4800 pixels wide, minimum.

If images are submitted with resolutions lower than these specifications, we may be unable to publish them, even if we accept the submission. Therefore, please make sure that the images submitted with your manuscript comply with these specifications.

Additional detailed information about digital art for publication can be found at links.lww.com/ES/A42

If a revision is requested, do not paste graphics into word processing documents; submit them as separate files in figure file format. NOTE: Before approving your submission, view the PDF that is created by the system to make sure images are easily legible for the editors and reviewers.

J. Manuscripts "In Press"

Please submit an electronic copy (Word, PDF) of any "In Press" manuscript that is cited in the reference list, labeled as "In Press, Reference # ___." (If a manuscript is not yet In Press, it must be removed from the reference list.)

K. Supplemental Digital Content

Authors may submit Supplemental Digital Content to enhance their article's text and to be considered for online-only posting. Supplemental Digital Content may include the following types of material: text documents, graphs, tables, figures, audio, and video.

Number and cite all Supplemental Digital Content consecutively in the text. In-manuscript citations should include the type of material submitted, should be clearly labeled as "Supplemental Digital Content," should include a sequential number, and should provide a brief description of the supplemental content. For example: "See table, Supplemental Digital Content 1, listing all medications used in this study." Each Supplemental Digital Content file must be composed to stand alone. For example, tables and figures must include titles, legends, and/or footnotes, following journal style, so the viewer can fully understand the supplemental content on its own. Production will not make any edits to the supplemental files; they will be presented as submitted.

For audio and video files, enter the author name, videographer, participants, length (minutes), and size (MB) of file in Editorial Manager. Authors should de-identify patients and remove patients' names from Supplemental Digital Content, obtain written consent from the patients or legal guardians, and submit written consent with the manuscript. Copyright for video or audio supplemental digital content will be required upon acceptance. For a list of acceptable file types and size limits, please review the publisher's requirements for submitting Supplemental Digital Content: links.lww.com/A142

L. Additional Information

1. **Units of Measurement**
   Use metric units. The units for pressures are mmHg or cmH2O. Diagonal slashes are acceptable for simple units, *e.g.*, mg/kg; when more than two items are present, negative exponents should be used, *i.e.*, ml · kg^{-1} · min^{-1} instead of ml/kg/min.
2. **Abbreviations**
   In order to enhance comprehension, the use of nonstandard abbreviations or acronyms is not allowed in the Abstract and is strongly discouraged throughout the body of the manuscript. Do not use jargon or nonstandard abbreviations to represent time or time points. Do not abbreviate single words. A list of standard abbreviations accepted by the journal may be found at Standard List of Abbreviations.
3. **Drug Names and Equipment**
   Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide manufacturer's name, city, state, and country. Be careful about the use of trademarked terms (*e.g.*, Thrombelastography™, TEG™, *etc.*).
4. **Data Reporting and Statistics**
   Detailed statistical methodology must be reported. Describe randomization procedures and the specific tests used to examine each part of the results; do not simply list a series of tests. Care should be taken with respect to: a) reporting of parametric vs. nonparametric data (median range (or percentiles) is preferred for nonparametric data); b) parametric vs. nonparametric statistical methods; c) corrections for multiple comparisons; d) false precision (summary statistics should not contain more significant digits than the original data); and e) variance reporting (standard deviation or 95% confidence interval, rather than standard error of the mean).
5. **Patient Identification**
   Do not use patients' names, initials, or hospital numbers. An individual (other than an author) must not be recognizable in photographs unless written consent of the patient or legal guardian has been obtained and is provided at the time of submission. Authors should obtain consent forms from the relevant institution(s).

M. Permissions

Permission is needed to publish any figure, abstract, portion of text, or table that has been previously published or copyrighted. Written permission must be obtained from the copyright holder. Authors are responsible for obtaining and uploading any needed permissions from the copyright holder upon submission of their manuscript and for providing proper attribution in the text of the manuscript. The following link may also be helpful: anesthesiology.pubs.asahq.org/public/rightsandpermissions.aspx

N. Language Editing Services

Articles submitted to the journal must be written with a solid basis of English language. If you need assistance in this area, listed below are a few companies that provide language and copyediting services. Use of an editorial service is at the discretion and cost of the authors and will not guarantee acceptance for publication in the journal. Please note: Appearance in the list of vendors does not represent endorsement by the publisher. Authors are encouraged to investigate each service on their own as well as seek out additional vendors offering similar services.

- American Journal Experts • Bio Science Writers • Boston BioEdit • Editage • Enago
- ScienceDocs • SPI Publisher Services • Scribendi • Text Check • The Medical Editor

Subject to change, Instructions as of October 2018.

Authors' General Checklist

Refer to specifics of article types as needed.

1. **COVER LETTER (optional)**

2. **TITLE PAGE (required for all submissions):**

   - ☐ Title
   - ☐ Authors' Information: First name, middle initial, last name, academic degree/s, institutional affiliation/s for each author
   - ☐ Corresponding Author: Name, complete mailing address, phone, fax and email address of the corresponding author
   - ☐ Clinical trial number and registry URL, if applicable
   - ☐ Prior Presentations: Meetings at which the work has been presented (name, exact date, location), if relevant
   - ☐ Acknowledgments: Complete information about individuals or organizations whose assistance is acknowledged
   - ☐ Word and Element Counts: Number of words in Abstract, in Introduction, and in Discussion; number of figures; number of tables; number of appendices, if any; and number of supplementary files, if any.
   - ☐ Abbreviated Title (Running Head): State the essence of the article (50 characters maximum) for all article types except Images in Anesthesiology, Letters to the Editor, and Mind to Mind
   - ☐ Summary Statement: A brief statement (35 words maximum) to be printed in the Table of Contents for Review Article, Clinical Focus Review, and Special Article submissions
   - ☐ Funding Statement: Sources of financial support for the work (including institutional support--do not leave blank)
   - ☐ Conflicts of Interest

3. **STRUCTURED ABSTRACT (300 words or fewer) as relevant to article type:**

   - ☐ Background
   - ☐ Methods
   - ☐ Results
   - ☐ Conclusions

4. **BODY OF MANUSCRIPT:**

   - ☐ Introduction
   - ☐ Materials & Methods
   - ☐ Statistics, if applicable
   - ☐ Results
   - ☐ Discussion
   - ☐ References
   - ☐ Figure Legends

5. **TABLES**

6. **APPENDICES, if any**

7. **FIGURES**

8. **SUPPLEMENTAL DIGITAL CONTENT, if any**

9. **COPIES OF LISTED IN-PRESS PAPERS, if any**

ANEXO 3 - Comprovante de submissão do manuscrito

Anesthesiology

Continuous positive airway pressure during induction of general anesthesia in children: a randomized clinical trial

--Manuscript Draft--

Manuscript Number:	
Full Title:	Continuous positive airway pressure during induction of general anesthesia in children: a randomized clinical trial
Article Type:	Original Investigation: Perioperative Medicine
Section/Category:	Clinical Trials 2019 (submission deadline: August 1, 2019)
Corresponding Author:	Jayme Marques dos Santos Neto, M.D. Recife, BRAZIL
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	Rebeca Gonelli Gonçalves, M.D.
	Thiago Gadelha B. Dos Santos, M.D.
	Flavia Augusta de Orange, Ph.D.
Order of Authors Secondary Information:	
Suggested Reviewers:	Alan Jay Schwartz, M.D., M.S.Ed The Children's Hospital of Philadelphia Because his area of interest is pediatric anesthesia
	Allan F. Simpao, M.D., M.B.I. The Children's Hospital of Philadelphia and the University of Pennsylvania Because of his expertise is in pediatric anesthesia.
Opposed Reviewers:	