THE INFLUENCE OF REMIFENTANIL
AND REMIFENTANIL-PLUS-SEVOFLURANE-CONTROLLED
HYPOTENSION ON MEAN ARTERIAL PRESSURE
AND HEART RATE IN CHILDREN

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Abstract: The aim of the study is to determine the influence of remifentanil
and remifentanil-plus-sevoflurane-induced anaesthesia on mean arterial pressure
and heart-rate during controlled hypotension in children and to evaluate the quality of the
operative field.

Methods: 30 children, ASA I physical status were scheduled for middle ear
microsurgery for cochlear implantation and divided into 2 groups:
R group (15 children who received remifentanil as a hypotensive agent during
general anaesthesia).
R + S group (15 children who received remifentanil and sevoflurane as hypo-
tensive agents together to reach the hypotensive level during general anaesthesia).
The hypotensive level was defined as 20% decrease of baseline MAP.
We used oral medication for sedation (1 mg/kg Flormidal), 10 mg/kg parace-
tamol rectally for postoperative analgesia.
Two variables were measured during the anaesthesia: MAP and HR at five
time intervals.
We also measured the duration of hypotension, the time to reach a hypotensive
level and the duration of anaesthesia and surgery (inmins).
The quality of the surgical field in terms of dryness was rated every ten
minutes by the surgeon who used a six-point scale, 0–5 scale (0 = no bleeding, visually
bloodless field; 5 = uncontrolled bleeding).

Results: Demographic analyses showed that 13 of the patients were female, 17
of them were male, with an age-range of 4.75 ± 3.2 years in the R group of patients and
3.5 ± 4.1 in the R + S group of patients.
Duration of hypotension was 135 ± 4 minutes (R) and 120 ± 3 minutes (R + S). Duration of anaesthesia was 160 ± 10 minutes (R) and 140 ± 9 minutes (R + S). The duration of surgery was 150 ± 5 minutes (R) and 130 ± 4 minutes (R + S). The time to reach hypotensive level was shorter in R + S group (5 ± 1 minutes) than R group (7 ± 6 minutes).

There was no statistically significant difference in MAP values measured at T1, T2, T3 and T4 time intervals between the two groups of patients (R and R + S group). We achieved hypotensive anaesthesia levels of MAP in both group of patients.

The influence of anesthesia on HR was analysed at the same time intervals.

In T2 time interval (30 minutes after the induction of anaesthesia), HR values in R group patients were statistically significantly higher than referent hypotensive values in the R + S group of patients (70–80 bpm).

We could see the same result of HR values at T3 and T4 time intervals (90 and 120 minutes after the induction) in R group patients compared with HR values in the R + S group. We achieved a hypotensive level of HR (70–80 bpm) only at R + S group of patients, which means that remifentanil in combination with sevoflurane is an excellent combination for maintaining hypotension during general anaesthesia.

The lowest hypotensive level of HR was measured 120 minutes after the induction of anaesthesia in the R + S group of patients (69 bpm).

Remifentanil and remifentanil in combination with sevoflurane are effective in inducing consistent and sustained controlled hypotension in children undergoing middle ear microsurgery.

**Key words:** remifentanil, sevoflurane, controlled hypotension, mean arterial pressure, heart rate, children.

**Introduction**

Controlled hypotension is defined as a reduction of the systolic blood pressure to 80–90 mmHg, a reduction of mean arterial pressure (MAP) to 50–65 mmHg or a 20% reduction of baseline MAP during general anaesthesia. The primary advantages of this technique are: minimization of surgical blood loss and better surgical visualization.

The history of controlled hypotension in paediatric surgery started in July 1955, when Dr. Sheila Anderson used arfonad (a ganglion blocker) to induce hypotension in children [14].

New techniques of controlled hypotension subscribe to the use of the natural hypotensive effect of the anesthetic drug with regard to the definition of the ideal hypotensive agent. It must be easy to administer, have a short onset time, an effect that disappears quickly when administration is discontinued, a rapid elimination without toxic metabolites, negligible effects on vital organs, and a predictable and dose-dependent effect.
Inhalation agents (isoflurane, sevoflurane) provide the benefit of being hypotensive agents at clinical concentrations [10].

A combination treatment of remifentanil with either propofol or an inhalation agent (isoflurane, desflurane or sevoflurane) at clinical concentrations is the most recent satisfactory technique [3].

Several different agents have been used with children to provide controlled hypotension including direct acting vasodilators, but they have many adverse effects. Adverse effects incite authors to seek a new agent which would correspond to the ideal agent for controlled hypotension. Recently, remifentanil, an ultra-short-acting μ-agonist opioid receptor, has demonstrated its ability in inducing controlled hypotension and in achieving a bloodless operative field with no need for additional potent hypotensive agents and with no described adverse effects on children when combined with sevoflurane [2].

Indicators for the hypotensive level of general anaesthesia are the level of MAP and HR.

MAP has to decrease by 20% from baseline values and HR has to decrease 70–80 bpm if patients are to achieve moderate hypotensive level (3–5-year old children).

The aim

1. To determine whether general anaesthetics (remifentanil and remifentanil in combination with sevoflurane) can induce controlled hypotension in children undergoing middle ear microsurgery, without using any other hypotensive drug.

2. To evaluate the effect of the quality of the operative field (using remifentanil and remifentanil plus sevoflurane as hypotensive agents) that is necessary for successful middle ear microsurgery.

3. To determine the influence of remifentanil or remifentanil-plus-sevoflurane induced anaesthesia on mean arterial pressure and heart-rate during controlled hypotension in children.

Material and methods

In 30 children, ASA I (American Society of Anesthesiology) physical status was scheduled on middle ear microsurgery for cochlear implantation. After adequate information was provided, the parents signed agreement form for operative intervention and anesthesia technique.
All patients were operated at the ENT University Clinic in Skopje, over a period of six years. They were divided into 2 groups:

– R group (15 children who received remifentanil as hypotensive agent during general anaesthesia)

– R + S group (15 children who received remifentanil and sevoflurane as hypotensive agents to reach the hypotensive level during general anaesthesia).

The children were admitted on the day before surgery and fasted for at least five hours prior to surgery. All children received an oral medication for sedation (1 mg/kg flormidal) half an hour before anaesthesia.

Postoperative analgesia was provided by 10 mg/kg rectal paracetamol every 8 hours (according to VAS – visual analogue scale).

Two haemodynamic variables were measured during the anaesthesia:

• Noninvasive determination of mean arterial blood pressure (MAP) mmHg

• Heart-rate (HR) beats per minute (bpm).

These variables were recorded continuously on a General Electronics Monitor every 5 minutes. Analysis was performed at 5 time intervals:

T0 – preoperative value (baseline value)
T1 – 30 minutes after the induction of anaesthesia
T2 – 60 minutes after the induction
T3 – 90 minutes after the induction
T4 – 120 minutes after the induction
T5 – the end of the operation

We also measured the duration of hypotension, the time to reach a hypotensive level and the duration of anaesthesia and surgery (in minutes).

Quality of the surgical field, in terms of blood loss and dryness, was rated every ten minutes by the attending surgeon who was unaware of the pharmacological procedure and treatments, using a six-point scale, 0–5 scale (0 = no bleeding, visually bloodless field; 5 = uncontrolled bleeding) [7].

Protocol for anaesthesia

The R group of patients was induced with Propofol (2.5 mg/kg body weight), endotracheal intubation was facilitated with rocuronium bromide (0.5 mg/kg b.w.) and maintained with remifentanil (see to Table 1).
Table 1

Infection rate (ml/h) of continuous infusion of remifentanil in concentration 25 μg/ml

<table>
<thead>
<tr>
<th>μg/kg/min</th>
<th>10 kg</th>
<th>20 kg</th>
<th>30 kg</th>
<th>40 kg</th>
<th>50 kg</th>
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<tr>
<td>0.0125</td>
<td>0.3</td>
<td>0.6</td>
<td>0.9</td>
<td>1.2</td>
<td>1.5</td>
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<tr>
<td>0.025</td>
<td>0.6</td>
<td>1.2</td>
<td>1.8</td>
<td>2.4</td>
<td>3.0</td>
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<tr>
<td>0.05</td>
<td>1.2</td>
<td>2.4</td>
<td>3.8</td>
<td>4.8</td>
<td>6.0</td>
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<tr>
<td>0.075</td>
<td>1.8</td>
<td>3.6</td>
<td>5.4</td>
<td>7.2</td>
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<td>0.1</td>
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<tr>
<td>0.15</td>
<td>3.6</td>
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<tr>
<td>0.2</td>
<td>4.8</td>
<td>9.6</td>
<td>14.4</td>
<td>9.2</td>
<td>24.0</td>
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</table>

1/3 of the induction dose of rocuronium bromide was added every 20 minutes during the operation and it had to be avoided 20 minutes before making cochleostoma. Technician tested the cochlear implant electrodes by the presence or not of a stapedial reflex and rocuronium had to be removed from the circulation to ensure the testing.

The R + S group of patients was induced with Propofol (2.5 mg/kg body weight), endotracheal intubation was facilitated with rocuronium bromide (0.5 mg/kg b.w.) and maintained with remifentanil (see to Table 1) and sevoflurane (inan adequate concentration for reaching the hypotensive level of mean arterial pressure). Rocuronium was added by the same protocol as for group R.

The children breathed through an endotracheal tube connected to a semi-closed anaesthetic circuit. Gas flow into the anaesthetic circuit was 2 l/min. We were using a Julian machine for anaesthesia.

Inspiratory and expiratory concentrations of carbon dioxide, sevoflurane and oxygen were measured using the same anaesthesia machine.

The endotracheal tube allowed controlled ventilation which was adjusted to end tidal CO₂ concentration of 35 mm Hg and to ensure SpO₂ over 97% with 50% nitrous oxide in oxygen.

Anaesthetics were delivered in order to induce controlled hypotension, considered effective when MAP reached the target: blood pressure decrease by 20% from the preoperative (baseline) values of MAP. After reaching the hypotensive level, the infusion rate was adapted in order to maintain the hypotension during the whole operative procedure.
Children assigned to the remifentanil group (R) received 1 μg/kg bolus dose of remifentanil intravenously (i.v.) in 30–60 sec, followed by a continuous infusion of remifentanil according to body weight (Table 1) until MAP decreased to hypotensive level. After that the infusion rate was adapted to maintain hypotension at this level.

Children assigned to the second group (R + S) received a continuous i.v. bolus infusion of remifentanil at a rate of 1 μg/kg remifentanil in 30–60 sec, followed by a continuous infusion of remifentanil according to body weight (Table 1) and sevoflurane (vol%) in a dose until MAP decreased to hypotensive level. After reaching the hypotensive level, the infusion rate of remifentanil and vol% of sevoflurane were adapted to maintain hypotension at the same hypotensive level.

All the drugs that we used during the operation were discontinued after the end of surgery.

Continuous infusion of remifentanil was stopped 2 minutes after the electronic testing (stapedial reflex testing) of the cochlear implant electrodes activity. Sevoflurane was excluded from the semi-closed anaesthetic circuit when the operative intervention was finished and an electronic device was put on the skin for electronic testing.

All patients spent the postoperative period in the recovery room. The monitoring in the recovery room included MAP and HR values, SpO₂ and analgesia (VAS scale of analgesia)

No surgical stress was applied until initiating hypotension. We measured the time that was needed to reach the hypotensive level in both groups of patients. Direct visual evaluation of the surgical field was performed from T0 every 10 minutes until the end of surgery.

Statistical analysis

• Analysis of Variance for repeated measures,
• Newman-Keuls test for Post-hoc analysis,
• Multivariate tests for repeated measure (Sigma-restricted parameterization for Effective hypothesis decomposition).

The threshold for statistical significance was taken as \( p < 0.05 \).

Results

Demographic analyses showed that 13 patients were female, 17 of them were male with an age of 4.75 ± 3.2 years in the R group of patients and 3.5 ± 4.1 in the R + S group of patients.
Duration of hypotension was 135 ± 4 minutes (R) and 120 ± 3 minutes (R + S). Duration of anaesthesia was 160 ± 10 minutes (R) and 140 ± 9 minutes (R + S). The duration of surgery was 150 ± 5 minutes (R) and 130 ± 4 minutes (R + S). The time to reach hypotensive level was shorter in the R+S group (5 ± 1 minutes) than the R group (7 ± 6 minutes). The end tidal concentration of sevoflurane was 2 vol% (mean value ± SE) in the R + S group of patients.

Results from repeated measures of MAP values are given in Graphic 1.

There is no statistically significant difference in MAP values measured at T1, T2, T3 and T4 time intervals between the two groups of patients (R and R + S group). We achieved hypotensive anaesthesia levels of MAP in both groups of patients.

The Post-hoc analyses of MAP values using the Newman-Keuls test at R and R + S group are shown in Table 2.
Post-hoc analysis of HR in both groups of patients are given in Table 3.

Table 3

Post-hoc analysis of HR in both groups of patients

<table>
<thead>
<tr>
<th>Newman-Keuls test</th>
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<td>Groups</td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T4</td>
<td>T5</td>
<td>T0</td>
<td>T1</td>
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<tr>
<td>T0</td>
<td>1.000015*</td>
<td>0.001015*</td>
<td>0.000010*</td>
<td>0.000020*</td>
<td>0.01-0.922</td>
<td>0.001-0.192</td>
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<td>0.01-0.922</td>
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<td>T1</td>
<td>0.000015*</td>
<td>0.001015*</td>
<td>0.000010*</td>
<td>0.000020*</td>
<td>0.01-0.922</td>
<td>0.001-0.192</td>
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<td>T2</td>
<td>0.000015*</td>
<td>0.001015*</td>
<td>0.000010*</td>
<td>0.000020*</td>
<td>0.01-0.922</td>
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<td>T3</td>
<td>0.000015*</td>
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<td>0.000020*</td>
<td>0.01-0.922</td>
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<td>T4</td>
<td>0.000015*</td>
<td>0.001015*</td>
<td>0.000010*</td>
<td>0.000020*</td>
<td>0.01-0.922</td>
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<td>T5</td>
<td>0.000015*</td>
<td>0.001015*</td>
<td>0.000010*</td>
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<td>R+S</td>
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<td>T1</td>
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<td>T2</td>
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<td>T3</td>
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<td>T4</td>
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<td>T5</td>
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<td>0.000010*</td>
<td>0.000020*</td>
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</table>

*p < 0.05

The influence of anaesthesia on HR was analysed at the same time intervals.

In T2 time interval (30 minutes after the induction of anaesthesia), HR values in the R group of patients were statistically significantly higher than the referent hypotensive values in the R + S group of patients.

We can see the same result of HR values at T3 and T4 time intervals (90 and 120 minutes after the induction) in the R group of patients compared with the HR values in the R + S group. We achieved hypotensive level of HR (70–80 bpm) only in the R + S group of patients, which means that remifentanil in combination with sevoflurane is a good combination for maintaining hypotension during general anaesthesia.
The lowest hypotensive level of HR was measured 120 minutes after the induction of anaesthesia in the R + S group of patients (69 bpm).

The relations between HR and analysed time intervals between the two groups of patients are given in Graphic 2.

There is a significant difference between the two groups of patients at T4 time interval (the lowest value of HR).

Results from evaluation of the quality of the operative field (descriptive parameter) showed that the quality of the surgical field was 3 (satisfactory conditions) in both groups of patients.

**Discussion**

Blood pressure monitoring is a recommended standard of care by the American Society of Anesthesiology (ASA) and pediatric anesthesiologists routinely monitor the blood pressure of their patients, but there is no robust definition of hypotension in any of the paediatric anaesthesia texts or journals. For
that purpose, members of the Society of Pediatric Anesthesia (SPA) and the Association of Paediatric Anaesthetists (APA) of Great Britain and Ireland designed a questionnaire-based survey of paediatric anesthesiologists to determine the blood pressure ranges and thresholds used to define induced hypotension during general anaesthesia.

About 76% of respondents indicated that a 20–30% reduction in baseline systolic blood pressure (SBP) indicates significant hypotension in children under anaesthesia [13]. We were using a safety hypotensive level of 20% decrease of MAP.

Most respondents (86.7%) used mean arterial pressure (MAP) rather than systolic blood pressure (SBP) (72% responders) to define intraoperative hypotension. The mean SBP values for hypotension quoted by SPA members was about 5–7% lower across all paediatric age groups compared with values quoted by APA members ($p = 0.001$ for all age groups).

They concluded that there was a great variability in the blood pressure parameters used and the threshold used for defining and treating intraoperative hypotension among paediatric anaesthesiologists. We have no variability in MAP and HR values, because we define and achieved a 20% decrease of MAP as the hypotensive level of MAP.

Our results are similar to those of Degoute C.S. et al. [5] that the most recent satisfactory controlled hypotension technique in children is a combination of remifentanil with an inhalation agent (sevoflurane) at clinical concentrations. They compare the effect of controlled hypotension achieved by remifentanil and nitroprusside (combined with alfentanil) on middle ear blood flow (MEBF) and bloodless surgical conditions. Controlled hypotension was achieved at the target MAP of 50 mmHg within 121 ± 21 sec and 62 ± 9 sec for remifentanil and nitroprusside respectively. The time to reach hypotensive level in both groups of patients is very short, because they anaesthetized all the children with sevoflurane.

MEBF decreased by 22 ± 4 and 20 ± 6% (remifentanil and nitroprusside group). The surgical field rating was good.

They concluded that remifentanil combined with sevoflurane in children enabled controlled hypotension, reduced MEBF and provided good surgical conditions for middle ear surgery with no need for additional use of a specific hypotensive agent.

Discussing the adverse effects of controlled hypotension, they had no postoperative, circulatory, neurological or metabolic complications in any patient. We had no adverse effects in children (extreme hypotension or HR reduction) when we combined remifentanil with sevoflurane.
Brown TCK. [2] published his early experiences of vasodilators and hypotensive anesthesia in children in 2012. His experience is that blood pressure could be reduced by a vasodilator such as sodium nitroprusside (a short-acting, vascular smooth muscle relaxant) or phenoxybenzamine (a long-acting α adrenoceptor antagonist). A less desirable alternative to lowering blood pressure could be to reduce cardiac output by suppressing myocardial contractility using a β(1) adrenoceptor antagonist or an inhalational agent such as isoflurane. We had no cardiac activity suppression (heart-rate decrease of more than 69bpm) when we used sevoflurane for inducing and maintaining hypotension in children (end-tidal concentration of sevoflurane of 2 vol%).

Conclusion

Remifentanil and remifentanil in combination with sevoflurane are effective in inducing consistent and sustained controlled hypotension in children undergoing middle ear microsurgery.

The onset of controlled hypotension achieved as the target of 20% decrease of MAP is faster if remifentanil is combined with sevoflurane.

Remifentanil and sevoflurane are effective anaesthetics in reducing MAP and HR due to hypotensive level in children with satisfactory operative conditions for the surgeon.

REFERENCES


Резиме

ВЛИЯНИЕТО НА РЕМИФЕНТАНИЛ И РЕМИФЕНТАНИЛ ПЛУС СЕВОФЛУРАНЕ КОНТРОЛИРАНА ХИПОТЕНЗИЯ ВРЗ СРЕДНИЯТ АРТЕРИСКИ ПРИТисОК И ПУЛСОТ КАЈ ДЕЦА

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Апстракт: Целта на студиjата e да се одреди влиjанието на remifentanil и remifentanil плус sevoflurane индуцирана анестезиjа врз средниjот артериски притисок и пулсот за време на контролирана хипотензия каj дeца, како и да се евалуира оперативното поле за време на анестезиjата.

Приложни, Одг. бил. мед. науки, XXXIII/1 (2012), 171–185
Метод: 30 деца со ASA I статус беа подложени на микрохирургија на средното уво за кохлеарна имплантација. Тие беа поделени во 2 групи:

R група (15 деца кoi добија remifentanil како хипотензивно средство за време на општа аnestezија).

R + S група (15 деца кoi добија remifentanil и sevofluran како хипотензивно средство за време на општа аnestyзија).

Хипотензивното ниво коеншто требааше да се постигне беше 20% намалување на средниот артериски притисок (MAP) од базалната вредност.

Користувме орална премедикација (1 mg/kg flormidal) и 10 mg/kg paracetamol ректално за постоперативна аналгезија.

За време на аnestyзијата беа мерени две варијабли: среден артериски притисок и пулс. Исто така беше мерено времетраењето на аnestyзијата, времето кое беше потребно за да се постигне хипотензија и траењето на оперативната интервенција во минути. Квалитетот на оперативното поле беше одредуван на секои десет минути со помош на скала од 0–5 (0 = нема крвавење, 5 = ноконтролирано крвавење).

Резултати: Демографските податоци покажаа дека 13 пациенти беа женски, а 17 пациенти беа макси деца, на возраст од 4,75 ± 3,2 години кaj R групата на пациенти и 3,5 ± 4,1 години R + S групата на пациенти.

Времетраењето на хипотензијата беше 135 ± 4 минути (R) и 120 ± 3 минути (R + S). Времетраењето на аnestyзијата беше 160 ± 10 минути (R) и 140 ± 9 минути (R + S). Времетраењето на хируриската интервенција изнесуваше 150 ± 5 минути (R) и 130 ± 4 минути (R + S). Времето за кое се постигна хипотензивно ниво беше пократко кај R + S групата (5 ± 1 минута) отколку кај R групата (7 ± 6 минути).

Не постоеше статистички значаен разлика помеѓу вредностите на MAP во T1, T2, T3 и T4 временските интервали помеѓу двата групи на испитаници (R и R + S групите). Ниие постигнавме хипотензивно ниво на MAP кај двете испитувани групи.

Влиянето на аnestyзијата врз пулсот беше анализирано во исти временски интервали.

Во T2 временскиот интервал (30 минути по вовед во аnestyзија) вредноста на пулсот кај R групата е статистички значаен повисока споредена со референтната хипотензивна вредност на пулсот на R + S групата на пациенти (70–80 удари/минута). Истиот резултат се добива и во T3 и T4 временскиот интервал (90 и 120 минути по вовед во аnestyзија) кај R групата на пациенти споредена со пулсот кај R + S групата. Хипотензивното ниво на пулсот (70–80 удари/минута) го постигнавме само кај R + S групата, што значи дека remifentanil во комбинација со sevofluran е одлична комбинација за одржување на хипотензијата за време на општа аnestyзија.

Најниското хипотензивно ниво на пулсот беше измерено 120 минути по вовед во аnestyзија кај R + S групата (69 удари/минута).
Remifentanil и remifentanil во комбинација со sevoflurane се ефективни средства за индуцирање и одржување на контролирана хипотензија кај деца за оперативни микрохирургиски интервенции на средно уво.

Ключни зборови: remifentanil, sevoflurane, контролирана хипотензија, среден артериски притисок, пулс, деца.

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