Comparison of propofol-ketamine versus propofol-remifentanil in children anaesthetized for gastroscopy

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Abstract

Background: The search for ideal anaesthesia is still an open research issue. The aim of the study was to evaluate and compare two methods of general anaesthesia with preserved own breath – propofol with ketamine and propofol with remifentanil – in children anaesthetized for gastroscopy.

Methods: The study included 90 children enrolled for elective endoscopy of the upper gastrointestinal tract under general anaesthesia. The patients were randomized to one of two groups: Group K consisted of children anesthetized with propofol and ketamine, Group R included children anesthetized with propofol and remifentanil. Parameters monitored during anaesthesia were induction time, respiratory and circulatory parameters, adverse events, waking time and the child's condition after regaining consciousness.

Results: The groups differed significantly in time of induction of anaesthesia (Group K 3 ± 1 min vs. Group R 4 ± 2.5 min; $P < 0.001$), waking time (Group R 4 ± 4.5 min vs. Group K 6 ± 5 min; $P < 0.01$), condition of the child after regaining consciousness (Group R 90.9% calm, Group of K 54% confused; $P < 0.001$) and evaluation of test conditions in the opinion of the gastroenterologist (in favour of Group K; $P < 0.05$).

Conclusions: Both methods of anaesthesia presented in the paper are safe and can be used in children to perform endoscopy. Combining propofol with ketamine allows fast induction of anaesthesia and creates very good conditions for the examination. Combining propofol with remifentanil allows fast and full return of consciousness after anaesthesia.

Key words: gastroscopy, anaesthesia, paediatrics, paediatric anaesthesia.

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The ideal method of anaesthesia is characterized by safety, depth of anaesthesia appropriate to the force of the stimuli from the operating field, rapid waking time, and providing good conditions for the examiner. Searching for such anaesthesia and its refinement remain an open research subject. Treatments that require anaesthesia include endoscopic, diagnostic and therapeutic procedures in paediatric gastroenterology. Most children require deep sedation or general anaesthesia [1, 2]. Sedatives, intravenous anaesthetic agents and analgesics are used for general anaesthesia with preserved spontaneous breathing. Synergistic effects of these drugs result in dose reduction, and thus reduce the likelihood of undesirable effects. Due to different mechanisms of action and properties of individual drugs, their appropriate combination, adequate dosage, choice of drugs adjusted to individual patient needs and type of procedure allow for safe anaesthesia. Short-term hypoxia occurs in 2 to 20% of children undergoing the discussed anaesthesia [3, 4]. There are not many publications that assess respiratory function on the basis of gasometry during anaesthesia with preserved spontaneous breathing.

The study is designed to answer the following questions: Is anaesthesia using ketamine or remifentanil with continuous propofol infusion safe in children undergoing gastroscopy? Can one of the tested methods of anaesthesia be considered superior after the analysis of the outcomes?

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METHODS

The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice. All children participating in the project and their caregivers were informed about the conditions of the study and its purpose. The consent of the parent or legal guardian and of the child (if the child was 16 or under 16 and was able to express his/her opinion consciously) was required for participation in the study and data processing.

The study included 90 children with ASA I status, who were enrolled for elective endoscopy of the upper gastrointestinal tract under general anaesthesia (see flow diagram, Figure 1). Following randomization and blinding, participants were assigned to either the study group based on a random number table and their study identification number, which correlated with the order in which they were enrolled in the study. Randomization was performed by a nurse who was not associated with anaesthesia. The study was single-blind and the anaesthetist knew which drugs were administered. Patients, their parents and endoscopists were unaware to which group the study subject belonged.

Interventions

The patients were randomized to one of two groups: Group K consisted of children anaesthetized with propofol and ketamine, and Group R included children anaesthetized with propofol and remifentanil. In Group K the first drug was ketamine administered intravenously at a dose of 1.5 mg kg^{-1}, followed immediately by a single intravenous dose of propofol 1.5 mg kg^{-1}. Subsequently, a continuous infusion of propofol at a dose of 6 mg kg^{-1} h^{-1} was administered through an intravenous cannula. In Group R, remifentanil infusion at a dose of 0.1 μg kg^{-1} min^{-1} was administered through an intravenous cannula, followed by a single intravenous dose of propofol 1.5 mg kg^{-1}. Next, a continuous infusion of propofol at a dose of 6 mg kg^{-1} h^{-1} was administered through an intravenous cannula. If necessary (child movement, awakening), a bolus of propofol at a dose of 0.5 mg kg^{-1} was administered intravenously in both groups. The duration of induction was measured with a timer from the moment of ketamine administration in Group K and initiation of remifentanil infusion in Group R to the moment of achieving the level of anaesthesia allowing the endoscope to be inserted without the child moving (Table 1).

Outcomes

All patients were monitored for: time of induction of anaesthesia (minutes) after ketamine administration in Group K or remifentanil in Group R until obtaining the level of anaesthesia allowing the endoscope to be inserted; number of attempts until the endoscope was finally inserted so that the examination could be carried out without the child moving; number of additional propofol doses; pain during propofol administration (yes/no scale); duration of gastroscopy (in minutes): time from endoscope insertion to its removal; waking time (in minutes) from the time of drug discontinuation to the moment the patient opened his/her eyes; state of consciousness of the child immediately after gastroscopy and after being transported to the Recovery Room, assessed on a three-level scale: conscious with contact (orientation in place and time relevant

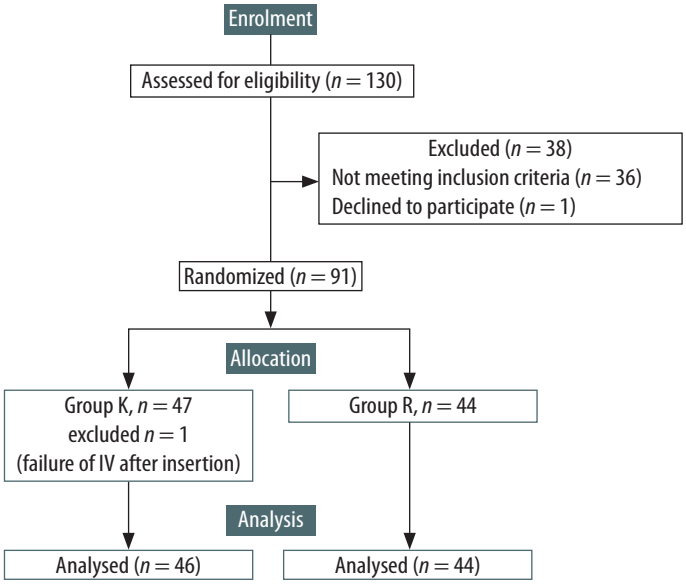


FIGURE 1. Flow diagram

TABLE 1. Standard pharmacotherapy in both groups, including intervention doses

Group K	Group R
Induction	Induction
Ketamine *i.v.* 1.5 mg kg^{-1}	Remifentanil *i.v.* 0.1 μg kg^{-1} min^{-1}
Propofol *i.v.* 1.5 mg kg^{-1}	Propofol *i.v.* 1.5 mg kg^{-1}
Maintenance of anaesthesia	Maintenance of anaesthesia
Propofol infusion 6 mg kg^{-1} h^{-1}	Propofol infusion 6 mg kg^{-1} h^{-1} + remifentanil infusion 0.1 μg kg^{-1} min^{-1}
If necessary, an additional dose of propofol *i.v.* 0.5 mg kg^{-1}	If necessary, an additional dose of propofol *i.v.* 0.5 mg kg^{-1}

to child's age, logical response to simple questions), conscious without contact (open eyes, disorientation in place and time, lack of response to simple questions) and unconscious (closed eyes, lack of response to commands); behaviour of children after recovery of consciousness assessed on a two-level scale: serene/calm; confused/agitated; desaturation (SaO_2 < 90%), apnoea (no breath > 10 seconds), bronchospasm (activation of additional respiratory muscles, abnormal respiratory murmurs); salivation assessed on a three-level scale: absent/slight/increased; oxygen partial pressure (pO_2) in mm Hg, carbon dioxide partial pressure (pCO_2) in mm Hg and pH in capillary gasometry taken at the end of the examination, normocapnia was at a pCO_2 value of 35–45 mm Hg (5–6 kPa); heart rate, arterial blood pressure measured noninvasively – at four time points: before induction of anaesthesia, after induction of anaesthesia, 10 minutes after induction of anaesthesia, on admission to the recovery room; saturation was monitored continuously; conditions of the examination in the opinion of the gastroenterologist performing the procedure, evaluated on a three-level scale: excellent/good/difficult; subjective evaluation of anaesthesia by the patient and/or his/her guardian based on the answers to the questions in the questionnaire.

Statistical analysis

The results were collected in an Excel spreadsheet and then exported to STATISTICA 12 software (StatSoft, Tulsa, USA), where statistical calculations were made. The following statistical tests were used: Shapiro-Wilk normality test; mean, standard deviation (SD), and minimum and maximum values were defined for quantitative variables with normal distribution; median, interquartile range (IQR), minimum and maximum values were defined for variables with a non-normal distribution; Student's *t*-test was used for unlinked variables to evaluate the statistical significance of differences between groups for normally distributed parameters; in the case where the parameters did not show qualities of normality, the nonparametric Mann-Whitney *U* test and the Kruskal-Wallis test were used; parameter correlation was checked by calculating Spearman's correlation coefficient *R*; the incidence of the examined features was also calculated (qualitative parameters); frequencies were compared with the χ^2 test; variance analysis and post hoc tests were used; *P*-value < 0.05 was statistically significant.

RESULTS

The characteristics of the study groups and the endpoint results are shown in Table 2. The studied groups were significantly different in: terms of duration of anaesthesia induction (group K 3 ± 1 min vs. group R 4 ± 2.5 min, $P < 0.001$); effectiveness of endoscope placement at the first attempt (the endoscope was inserted at the first attempt in 95.7% in Group K vs. 47.7% in Group K, $P < 0.001$); the need to administer an additional dose of propofol (10.9% of children in Group K required an additional propofol dose vs. 77.3% of children in Group R, $P < 0.001$), level of consciousness after arriving in the Recovery Room (conscious with contact: 69.6% in Group K vs. 93.2% in Group R, $P = 0.005$) and child's mood after regaining consciousness (cheerful: 54.3% in Group K vs. 90.9% in Group R, $P < 0.001$); waking time (6 ± 5 min in Group K vs. 4 ± 4.5 min in Group R, $P = 0.007$); conditions of the examination in the opinion of a gastroenterologist (excellent conditions: 60.9% in Group K vs. 29.5% in Group R, $P = 0.009$). Increased salivation occurred significantly more frequently in Group K ($P < 0.01$). Differences in the frequency of adverse events (apnoea, desaturation, bronchial spasm, vomiting) were statistically insignificant. The examined groups did not differ significantly in the gasometry, the partial pCO_2 was not significantly different ($P = 0.93$). Partial pCO_2 concentration in gasometry was normal in over 60% of children; in less than 40% of patients pCO_2 was elevated (max 60 mm Hg). There was no correlation between gasometry results and children's behaviour. Statistically significant differences in the selected haemodynamic parameters are shown on the graphs (Figures 2–4) and discussed.

DISCUSSION

Both methods of anaesthesia were safe, no patient required instrumental opening of the airways or assisted breathing. All patients were haemodynamically stable. Taking into account the short waking time and the absence of pCO_2 impact on the behaviour of the child after waking, it can be assumed that observed hypercapnia had no clinical implications. The waking time was satisfactory, and the behaviour of children after anaesthesia did not raise anxiety of their parents. The vast majority of gastroenterologists favourably evaluated the conditions of the examination.

Gul *et al*. [5] used remifentanil with propofol for the anaesthesia of children undergoing gastroscopy in a different way than the one discussed in the study. Remifentanil was given in a single dose of 0.25 μg kg^{-1} min^{-1} and propofol in a single dose of 2 mg kg^{-1}. All subjects had apnoea lasting for 26 seconds, on average. It was not accompanied by desaturation requiring intervention. Clinically significant episodes of hypotension and/or bradycardia were not observed. Also, the additional dose of propofol was lower than in our study, and the

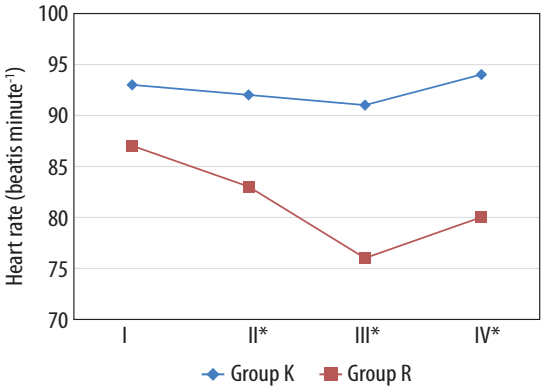
TABLE 2. Patient characteristics and outcome data

	Group K ($n = 46$)	Group R ($n = 44$)	*P*
Age (years, mean ± SD)	13.0 ± 9.0	12.0 ± 8.0	0.67
Male, *n* (%)	18 (39.1%)	14 (31.8%)	0.47
Duration of gastroscopy, minutes (median ± IQR)	9 ± 2	9 ± 2	0.78
Duration of anaesthesia induction (minutes, median ± IQR)	3 ± 1	4 ± 2.5	< 0.001
Endoscope successfully placed at the first attempt, *n* (%)	44 (95.7%)	21 (47.7%)	< 0.001
Need for an additional dose of propofol, *n* (%)	5 (10.9%)	34 (77.3)	< 0.001
Waking time, minutes (median ± IQR)	6 ± 5	4 ± 4.5	0.007
State of consciousness on admission to recovery room			0.005
Unconscious, *n* (%)	32 (69.6%)	1 (2.3%)	
Conscious without contact, *n* (%)	2 (4.3%)	2 (4.5%)	
Conscious with contact, *n* (%)	12 (69.6%)	41 (93.2%)	
Behaviour of child after regaining consciousness			< 0.001
Serene/calm, *n* (%)	25 (54.3%)	40 (90.9%)	
Confused/agitated, *n* (%)	21 (46.7%)	4 (9.15%)	
Adverse events			
Apnoea, *n* (%)	2 (4.3%)	6 (13.6%)	0.12
Desaturation, *n* (%)	3 (6.5%)	5 (11.4%)	0.42
Bronchospasm, *n* (%)	1 (2.2%)	1 (2.3%)	0.97
Vomiting, *n* (%)	2 (5.13%)	0	0.75
Carbon dioxide pressure, pCO_2 (mm Hg)			0.93
Median ± IQR	44 ± 4	44.5 ± 5	
Min–Max	34–57	27–60	
Oxygen pressure, pO_2 (mm Hg)			0.98
Median ± IQR	115 ± 101	136.75 ± 78	
Min–Max	67–349	55–341	
Conditions of the examination in the gastroenterologist's opinion			0.009
Excellent	60.9%	29.5%	
Good	32.6%	52.3%	
Difficult	6.5%	18.2%	
Child's condition after anaesthesia in the opinion of his/her parents			0.99
Calm	74%	81%	
Restless	18%	11%	
Tearful	8%	8%	

Group K – anaesthesia with propofol and ketamine, Group R – anaesthesia with propofol and remifentanil

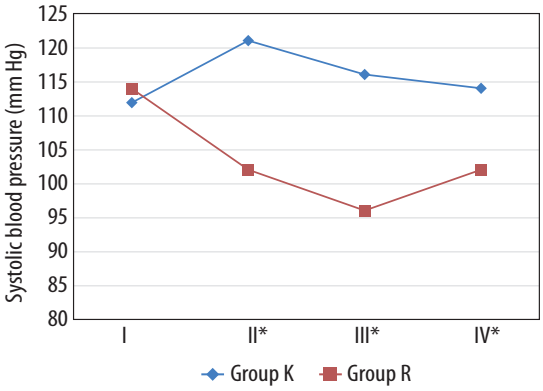
comfort of work was assessed by the gastroenterologists as very good. In our study, nearly half of the subjects in Group R required repeated attempts to insert an endoscope, which was clearly assessed by gastroenterologists as worse examination conditions compared to Group K. In the study of healthy young adults anaesthetized for dental procedures as well as in the population of young children anaesthetized for changing dressings, there was no difference in the assessment of the conditions of the procedure between propofol with ketamine or propofol with remifentanil [6, 7]. Perhaps it is because of the specifics of gastroscopy, during which endoscope insertion is one of the most difficult moments during the examination.

When assessing the two methods, the advantage of anaesthesia with ketamine can be demonstrated. When discussing advantages and disadvantages of the combination of propofol and ketamine, Green *et al*. asked the question: Why should we use two drugs if monotherapy is good? [8]. The results of numerous studies provided arguments in favour of combining the mentioned anaesthetics. In a randomized study of children aged 1–13, Akin



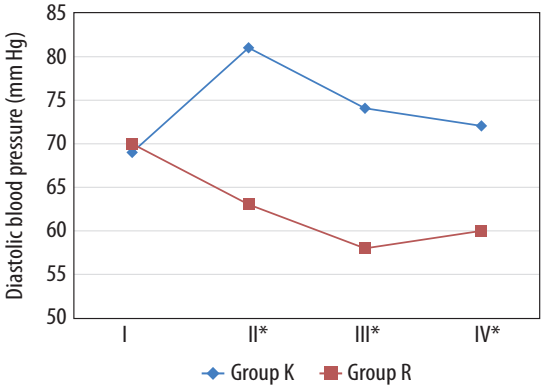
Group K – anaesthesia with propofol and ketamine
Group R – anaesthesia with propofol and remifentanil
I – measurement before induction of anaesthesia
II – measurement after induction of anaesthesia
III – measurement within 10 minutes after induction of anaesthesia
IV – measurement in the recovery room
*P-value < 0.05

FIGURE 2. Heart rate at four time points



Group K – anaesthesia with propofol and ketamine
Group R – anaesthesia with propofol and remifentanil
I – measurement before induction of anaesthesia
II – measurement after induction of anaesthesia
III – measurement within 10 minutes after induction of anaesthesia
IV – measurement in the recovery room
*P-value < 0.05

FIGURE 3. Systolic blood pressure at four time points



Group K – anaesthesia with propofol and ketamine
Group R – anaesthesia with propofol and remifentanil
I – measurement before induction of anaesthesia
II – measurement after induction of anaesthesia
III – measurement within 10 minutes after induction of anaesthesia
IV – measurement in the recovery room
*P-value < 0.05

FIGURE 4. Diastolic blood pressure at four time points

et al. compared monoanaesthesia with propofol only and propofol with low doses of ketamine. The starting dose of propofol in both groups was identical to that reported in the study, i.e. 1.5 mg kg^{-1}. The dose of ketamine was lower, i.e. 2.0 mg kg^{-1}. A group of children with anaesthesia using propofol alone required additional doses of the drug, and was characterized by apnoea and injection pain [9]. Both Kramer and Seol reported nearly double the time to the return of consciousness after using propofol and ketamine compared to propofol and remifentanil [6, 7]. These studies were conducted in two extremely different age groups (12–36 months of age and adults aged 18–24). Waking time following the administration of propofol with ketamine mainly depends on the mode of administration of ketamine (single dose versus continuous infusion). In the case of a single dose, a waking time of no more than 10 minutes has been reported in the available literature [9]. In our study, some children had a longer wake up time, which may be an argument for reducing the ketamine induction dose and propofol infusion dose used to maintain anaesthesia.

In Group K, more than 54% of children were confused and agitated after waking up. This was especially true for older children. This condition was transient and not remembered by the children or badly received by their parents. This is consistent with the study by Tosun *et al*., where dizziness and double vision were significantly more common in children anaesthetized with propofol and ketamine compared to propofol and opioid anaesthesia. Most patients did not have such complaints [11]. When ketamine is used, the possibility of psychomotor agitation, hallucinations, unpleasant dreams and dissociative states should be considered (one patient reported that she felt her fingers did not belong to her). Dolansky *et al*. discussed this broadly, pointing to increased incidence of this phenomenon with age and the possibility of exacerbation of psychosis in patients with existing mental disorders. In healthy children these conditions are rare, mild and easy to control [12, 13].

There are very few studies evaluating gasometric parameters or end-tidal pCO_2 concentration during anaesthesia with preserved spontaneous breathing in children anaesthetized with remifentanil with propofol or ketamine with propofol. One of the few such studies was conducted by Tsui *et al*., who used propofol with remifentanil in anaesthesia of neonates and children prior to magnetic resonance imaging. The respiratory rate decreased sig-

nificantly from 27 to 16 per minute, and the mean concentration of exhaled CO_2 increased from 38 to 43 mm Hg (5–6 kPa). Two children had desaturation but no intervention was needed [14].

Unlike propofol, ketamine causes a transient increase in blood pressure due to the inhibition of catecholamine uptake, which counteracts hypotension caused by propofol [15]. The results of haemodynamic analysis in Group K are consistent with references and confirm the advantages of the combination of propofol with ketamine to maintain haemodynamic stability [16–18]. The reduction in heart rate and blood pressure over time in Group R is due to the synergistic effects of propofol and remifentanil on the cardiovascular system [19].

According to the authors, the chronotropically negative effect of remifentanil is apparent and the reduction in heart rate in children is dependent on the individually variable susceptibility of the parasympathetic system [19].

The study was limited by the lack of one of the endoscopists. Gastroscopy was performed by three physicians, including two with extensive experience. The way of inserting the endoscope may have affected the need to deepen anaesthesia.

The second limitation was the lack of adherence to the time limit after initiating remifentanil infusion necessary for the drug to work, which could have had a significant effect on the results in Group R.

Accurate estimation of the drug dose, time and method of administration, taking into account the age of the child, may be a subject of further research.

CONCLUSIONS

In conclusion, both anaesthesia methods are safe, maintain respiratory function and have been favourably assessed by patients and their parents. The combination of propofol and ketamine offers quick induction of anaesthesia and provides very good test conditions while maintaining cardiovascular stability. The combination of propofol and remifentanil provides a fast waking time and cheerful mood after waking up. The choice of anaesthesia should be adjusted individually, depending on which endpoint will be given priority in a particular clinical situation.

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