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Original Article

All about ketamine premedication for children undergoing ophtalmic surgery

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Abstract: Ketamine is a non-barbiturate cyclohexamine derivative which produces a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment. One of the most important advantages of ketamine premedication is production of balanced sedation with less respiratory depression and less changes in blood pressure or heart rate. As its effects on intracranial pressure, the possible effect of ketamine on intraocular pressure has been controversial overtime. In this study, we aimed to demostrate all the advantages and possible side effects of ketamine premedication in 100 children with retinablastoma undergoing ophthalmic surgery. All the children were premedicated with ketamine 5 mg kg^{-1} 15 minutes before the examination orally and peroperative complications, reaction to intravenous catheter insertion, need for additive dose and intraocular pressures of children were recorded. We showed that ketamine administration orally is a safe and effective way of premedication for oncologic patients undergoing examination under general anaesthesia. The incidence of agitation, anxiety at parental separation and reaction to insertion of intravenous catheter was very low while adverse side effects were seen rarely. Intraocular pressure which is very important for most of the ophthalmic surgery patients remained in normal ranges.

Keywords: Ketamine, premedication, intraocular pressure, ophtalmic

Introduction

Perioperative period is a stressfull experience for both patients and their families. But this period often becomes extremely traumatic for younger patients. It is estimated that about 70% of all children exhibit significant stress and anxiety before surgery [1]. Extreme preoperative anxiety has been reported to result in negative postoperative outcomes [2]. So, preoperative management of anxiety is necessary in pediatric anesthesia.

Midazolam is a benzodiazepine with rapid onset of action and relatively short duration of action [3]. Currently midazolam is the most commonly used premedication [4] but but several studies have shown that satisfactory results are seen in only 60-80% of cases [5].

Ketamine is a non-barbiturate cyclohexamine derivative which causes dissociation of the cortex from the limbic system [6]. It produces a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment [3]. One of the most important advantages of ketamine premedication is production of balanced sedation with less respiratory depression and less changes in blood pressure or heart rate [7]. The major drawback of ketamine premedication about respiratory system seems to be increase in salivation and bronchial secretions which can lead to laryngospasm [8].

As its effects on intracranial pressure, the possible effect of ketamine on intraocular pressure (IOP) has been controversial overtime [9]. In early 1970s, Yoshikawa have reported ketamine to increase IOP significantly in children [10] but later studies [11-17] have shown ketamine not to raise IOP, therefore recommended its usage for ophthalmic procedures requiring sedation or anesthesia.

In this study, we aimed to demostrate all the advantages and possible side effects of ketamine premedication in children in a single group undergoing ophthalmic surgery.

Table 1. Face, legs, activity, cry, consolability (flacc) behavioral scale

Item	SCORE 0	SCORE 1	SCORE 2
Face	No particular expression or smile	Occasional grimace, frown, withdrawn or disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, or tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, or tense	Arched, rigid, or jerking
Cry	No cry	Moans, whimpers, or occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Table 2. Patient characteristics

Variables	n=100
Age (month)	30 (7-96)
Weight (kg)	13 (6-25)
Height (cm)	88 (72-100)
Comorbidity (dk)	0
Duration of operation (min)	20.74 (14-31)

Methods

After approval of the Hospital's Ethics Committee and parental written informed consent, 100 children with ASA status II, aged between 7 to 96 months, and undergoing examination under general anaesthasia due to retinoblastoma were included in the study. Patients with cardiovascular, pulmonary or neurologic diseases or current upper respiratory infection were excluded from the study.

All the children were premedicated with ketamine 5 mg kg^{-1} orally by the same anesthesilogist. 15 minutes after the premedication, they were seperated from their parents and taken to the operation room. Standard monitorization included pulse oximetry, non-invasive blood pressure and heart rate. Respiratory rates of children were also counted at each minute.

In preoperative period, the presence of agitation, tashycardia, nausea and vomiting, increase in salivation and reaction to intravenous catheter insertion were recorded. If the patient became agitated, intravenous catheter was placed with the help of sevoflurane induction.

Intraoperatively reactions (such as trying to turn head, closing eyes, moving arms and legs) to blepharostat, cryotherapy or laser usage, need for additive anesthetic dose and complications such as laryngospasm, hypocapnia, plugs due to increased salivation, arrythmia, skin eruption and anaphylaxis were observed. At the end of the operation, operation time was recorded and all the children were subsequently transferred to the recovery room.

In the recovery room, children were evaluated with Alderete scor at 10 minute intervals and early postoperative complications were recorded meanwhile. After two hours in the recovery room, all the patients were sent to the ward.

In the postoperative period, the time needed for tolerence of oral feeding was recorded by the nurses. Also FLACC (Face, Legs, Activity, Cry, Consolability) Behavioral Scale, nausea and voming were recorded at postoperative 30., 60. and 120. minutes. FLACC behavioral pain scale which has 5 behavioral categories as facial expression, leg movement, bodily activity, cry or verbalization, and consolability were rated on a scale of 0 to 2 to provide an overall pain score ranging from 0 to 10 (**Table 1**) [18]. In a recent study FLACC Behavioral Scale was shown to have excellent reliability and validity in assessing pain in children and critically ill adults [18].

At the end of the operation, parents and surgeon satisfaction were asked and the results were evaluated as "bad", "average", "good" or "very good".

The parents were asked if they recognised any behavioral changes, agitation or anger, witnessed an experience of nightmare, hallucination or enuresis at their children in the day of the operation and then 1, 2 and 30 days after operation with the help of a telephone conversation. Hallucinations were asked at both preoperative, peroperative and postoperative periods.

Statistical analyses were performed using SPSS for Windows 11.5 package program. Descriptive statistics were produced for a sin-

Table 3. Distribution of preoperative clinical properties

Variables	n=100
Agitation	11
Reaction to intravenous catheter	19
Sevoflurane endication	30
Secretion	12
Tachycardia	6
Nausea	1
Vomiting	0
Hallucination after premedication	5

Table 4. Distribution of intraoperative side effects and clinical properties

Variables	n=100
Secretion	2
Tachycardia	0
Vomiting	0
Laryngospasm	1
Reaction to blepharostat	
Eye closing	3
Arm movement	10
Head turning	2
Reaction to cryothrapy or laser	
Eye closing	1
Arm movement	5
Need for additive dose	21

Table 5. FLACC score and incidence of nausea and vomiting according to follow up time

Follow up time	FLACC	Nausea-Vomiting
30. min	0.13±0.37[a]	7 (7%)
60. min	0.07±0.26	4 (4%)
120. min	0.04±0.20[a]	2 (2%)

[a]The difference between 30. and 120. minutes is sitatistically significant (P=0.013).

gle patient group. Continuous variables were shown via median (minimum-maximum) volues, while observation number and proportions (%) were used for categorical variables. The difference between the VAS at different follow up times was evaluated via Wilcoxon Sign Test. McNemar test was used to examine if there was any significant difference between the prevalances at different follow up times. Statistical significance was assumed for P values < 0.05.

The study was approved by the X regional research ethics committee (Ref: 07/A123/456) and registered with EudraCT (ref: 2007: 123456: AA).

Results

In this study, 100 children were premedicated with ketamine and all the children were included in the statistical analysis. The characteris*tics* of the children and duration of surgical procedure were seen in **Table 2**.

The premedication was performed orally 15 minutes before the operation. In preoperative period side effects of ketamine administration were recorded at the operating room. The most commenly seen side effect of ketamine was increase in salivation (12 patients) which was followed by tachycardia (6 patients). Nausea was seen in only one patient whereas none of the patients vomited. In 11 patients agitation was seen at the separation from parents and 19 patients showed reaction against intraveous catheter insertion, so overall 30 patients needed for sevoflurane induction for venous access. The distribution of patients according to preoperative clinical properties is seen in **Table 3**.

Following the insertion of venous line, surgical operation started. Due to reaction to blepharostat, cryotherapy or laser usage, additive anesthetic doses were required in 21 of the patients. In 5 of the patients, intraoperative complications such as laryngospasm, increase in secreation and hallicunation were seen. The intraoperative data was seen in **Table 4**.

At the end of the operation, all the patients were sent to recovery room and observed for two hours. Nausea and vomiting were seen in seven of the patients at 30. minute and two of the patients at 120. minute postoperatively. FLACC score was 0.13±0.37 at 30. minute and 0.04±0.20 at 120. minute. The difference between FLACC score at 30. minute and FLACC skore at 120. minute was found to be significantly important (**Table 5**).

12 of the patients had right eye enucleation and 14 had left eye enucleation before this study. In the recovery room, patients' intraocular pressure (IOP) of both eyes were measured and the found levels were grouped as "under 10 mmHg", "between 10 and 20 mmHg" and "higher then 20 mmHg". The results are listed in **Table 6**.

Table 6. Distribution of IOP levels in both eyes

IOP	Right eye (n=88)	Left eye (n=86)
< 10 mmHg	6 (6.8%)	4 (4.7%)
10-20 mmHg	80 (90.9%)	80 (93.0%)
> 20 mmHg	2 (2.3%)	2 (2.3%)

Table 7. Distribution of the postoperative clinical properties

Variables	n=100
Postoperative hallucination	4
Parent satisfaction	
Average	1
Good	38
Very good	61
Surgeon satisfaction	
Good	13
Very good	87
Oral feeding time	60 (30-115)

Table 8. The incidences of behavioral changes, nightmare, hallicunation and enuresis at different follow up times

Follow Up day	Behavioral changes	Nightmare	Hallicunation	Enuresis
Day 0	16 (16%)[a,b,c]	6 (6%)	4 (4%)	3 (3%)
Day 1	7 (7%)[a]	3 (3%)	4 (4%)	6 (6%)
Day 2	5 (5%)[b]	5 (5%)	2 (2%)	5 (5%)
Day 30	5 (5%)[c]	9 (9%)	2 (2%)	7 (7%)

[a]The difference between day 0 and day 1 is statistically important (P < 0.05), [b]The difference between day 0 and day 2 is statistically important (P < 0.05), [c]The difference between day 0 and day 30 is statistically important (P < 0.05).

In both right and left eyes, the incidence of IOP higher that 20 mmHg after ketamine administration was not found to be statistically important.

At early postoperative period, four patients had hallucinations and no series complication was seen. Overall, 61 of the parents and 87 of the surgeons declared that level of the anesthetic procedure was "very good" and satisfactory (**Table 7**).

The presence of behavioral changes, nightmares, hallicunations and enuresis were asked at four different follow up times and it's found that the most commen postoperative side effect was behavioral changes. 16 of the patients had behavioral changes at the operation day and the number decreased to 5 after 30 days. The difference between the incidences of behavioral changes was found to be significantly important at all the specified follow up times (**Table 8**).

Discussion

This study demonstrates that oral ketamine is a safe and effective way of premedication for oncologic patients undergoing examination under general anaesthesia. The incidence of agitation, anxiety at parental separation and reaction to insertion of intravenous catheter was very low while adverse side effects such as increase in secretion, laryngospasm and vomiting were seen rarely. Intraocular pressure which is very important for most of the ophthalmic surgery patients remained in normal ranges. In the present study, ketamine premedication also decreased the anesthetic requirement of the children. 30 children needed sevoflurane induction while ketamine premedication provided a comfortable stuation for examination under general anesthesia at 70% of the patients.

The preoperative anxiety usually come from children's fear of separating from their parents, uncertainty related to anaesthesia, surgery and surgical outcome [1]. Extreme anxiety and stress before surgery has been reported to result in negative postoperative outcomes [2].

Three clinical phenomena have been described in children undergoing surgery: preoperative anxiety, emergence delirium, and new-onset postoperative maladaptive behavioral changes such as postoperative general anxiety, night time crying, enuresis, separation anxiety, apathy, withdrawal, and temper tantrum [2]. Kain and colleagues have also shown that increased preoperative anxiety in children is associated with postoperative pain and may hinder recovery [19]. Also it has been indicated that children with higher levels of preoperative anxiety were at 3.5 times higher risk for showing immediate postoperative period negative behavior as compared to less anxious children [20].

Over years, the interest for interventions directed at relieving chieldren's anxiety has increased. These interventions may be psychological, such as the presence of parents or information programs, or pharmacological, such as preanesthetic medication [21].

Currently midazolam is the most commonly used premedication [4, 22] and although it seems to meet most of the criteria, it is far from an ideal premedication. It causes an increased incidence of adverse effects such as postoperative behavior changes, cognitive impairment [23], paradoxical reactions, and respiratory depression [24]. Several studies have shown that satisfactory results are seen in only 60-80% of cases [5, 25, 26]. Also Griffith and colleagues have reported that at least 50% of children cry at the time of intranasal application, so intranasal midazolam premedication casuses significant distress and unpleasant experience to children [27]. Ketamine is a non-barbiturate cyclohexamine derivative which causes dissociation of the cortex from the limbic system [6]. It produces a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment [3]. Ketamine has a complex mechanism of action but its analgesic and neuroprotective effects are thought to be due to non-competitive antagonism of NMDA and agonism of μ-opiate receptors [28, 29].

Ketamine has 12% protein binding and high lipid solubility, so its distribution is extensive in the body and rapidly absorbed after intravenous, intramuscular, intranasal and oral administrations [30]. In a recent study, oral administration of ketamine 6 mg kg^{-1} for pediatric premedication have been shown to produce rapid onset of satisfactory sedation with appropriate amnesia and no cardiorespiratory side effects [31]. In current study, we prefer to use ketamine orally even in lower doses and in 89% of the patients we got excellant resulst at the parental separation within as short as 15 minutes. And only 19% of the patients showed reaction to insertion of intravenous catheter.

Audenaert and colleagues have shown that ketamin, whether given as alone or with other drugs, provides cardiovascular stability, so it can be used as an induction drug for patients with unstable cardiovascular physiology [32]. The resultant haemodynamic effect is thought to be a balance between a direct negative inotropic effect and central sympathetic stimulation [33].

In the present study, none of the patients had bradycardia whereas preoperative tachycardia was recorded at only one patient. The non invase blood pressures measured after the premedication were in normal ranges at all of the patients.

In previous studies, ketamine has been reported to increase pulmoner vascular pressure in both adults and children [33-35], but in a recent study Williams and colleagues have shown that ketamine does not increase pulmonary pressure significantly in spontaneously breathing children anesthetized with sevoflurane [36].

Becides, Shulman and colleagues have shown that kematine supports chest wall muscle tone and maintains functional residual capacity of the lung, so it has been reported not to cause a decrease in arterial blood oxygenation of children breathing room air spontaneously [37].

In our study, none of the patients decreased oxygen saturation due to decrease in respiratory rate. Only one patients had laryngospasm and needed ventilation support.

The major drawback of ketamine premedication about respiratory system seems to be the increase in salivation and bronchial secretions which can lead to laryngospasm [8]. Filatov and colleagues have reported that when compared with rectal diazepam and diclofenac premedication, oral ketamine premedication causes singlificantly higher scores of stridor in children undergoing adenoidectomy [8]. On the other hand, Gutstein and colleagues have compared placebo with oral ketamine 3 mg kg^{-1} and oral ketamine 6 mg kg^{-1} premedications and in this study the amout of oral secreations present in intubation were similar. The incidence of laryngospasm did not differ significantly among groups [31]. In our study, respiratory side effects due to ketamine premedication were minimal. Increase in secretion was seen only in 12 patients preoperatively and two patient at intraoperative period. As mentioned before, laryngospasm was recorded only in one patient at intraoperative period and needed ventilation support.

In the case-control and case-report studies of 1970s, ketamine have been reported to increase cerebral blood flow and intracranial pressure. So it was recommended to avoid ketamine usage in patients with head injuries and intracranial diseases [38-40]. Nevertheless very recently Filanovsky and colleagues have documentated several studies [41-43] reporting that ketamine did not cause a significant increase in intracranial pressure in head-injured patients. They have claimed that ketamine appears to be the perfect agent for the induction of head-injured patients [44].

Just like the effect on intracranial pressure, the possible effect of ketamine on intraocular pressure (IOP) has been controversial overtime [9]. In early 1970s, Yoshikawa have reported ketamine to increase IOP significantly in children [10]. In 1981, Norbury and colleagues have studied on 20 adult patients undergoing ophtalmic surgery and compaired the effects of inhalation anaesthesia versus flunitrazepam and ketamine combination on IOP. A significant decrease of IOP was reported in both groups [12]. In 1999 Frey and colleagues have compaired propofol and propofol-ketamine sedation on 66 patients undergoing cataract extraction and intraocular lens implantation surgeries. They have shown similar reductions in IOP after administration of the hypnotic dose of the study drugs in both groups [14].

In early 2000s, s(+)-ketamine which is an enantiomer of racemic ketamine reported to have double analgesic and anesthetic potency, less psychomimetic side effects, less salivation, less loading of substance and faster elemination, started to replace racemic ketamine in Europe [45]. In 2002 Becker and colleagues have studied on adult patients undergoing cataract surgery to observe the changes on IOP, but this time ketamine was compared with not only other drugs such as propofol and fentanyl, but also s(+)-ketamine. There were no significant difference on IOP among all groups. The have concluded that s(+)-ketamine seemed to be a safer choice of drug because of a high spontaneous breathing rate and lower concentration when compared to ketamine [15].

In 2007 Blumberg and colleagues have shown the effects of sevoflurane and ketamine premedications on IOP. The study was carried on children during examination under anesthesia and IOP was found significantly lower in the sevoflurane group. The resources have reported that IOP measured after ketamine sedation is more likely to represent the awake measurements [16].

In 2010 this time Jones and colleagues have shown the effects of sevoflurane and ketamine on IOP. Eight children with glaucoma undergoing examination under anaesthesia were included in the study. The children were premedicated with either intramuscular injection of ketamine 5 mg kg^{-1} or intravenous injection of ketamine 2 mg kg^{-1}. Later anaesthesia was maintained with sevoflurane. They have reported that sevoflurane lowered the IOP significantly compared with ketamine. The IOP was similar in subgroups of ketamine premedication [17]. In our study, totally 174 eyes were observed and in only four of them, IOP were found to be over 20 mmHg, but this incidence was not found to be statistically important. So we can say that oral ketamine 5 mg kg^{-1} premedication did not increase IOP over normal ranges at children with retinoblastoma.

As it is mentioned above, children with higher levels of preoperative anxiety were at 3.5 times higher risk for showing immediate postoperative period negative behavior as compared to less anxious children [20]. In our study, behavioral changes were seen in only 16% of the patients at the operation day. This ratio decreased to 5% after 2 days. The incidence of hallucinations were as low as 2% 30 days after the operation whereas the incidence of nightmares and the presence of enuresis increased slightly overtime. But this increase was not found to be statistically important. It should be indicated that all of these oncologic children underwent examinations or enucleation operation before. They all have history of anesthesia. So we can not determine if some of these adverse reactions result from recent anaesthesia and hospital experiences or not.

Currently midazolam is the most commonly used premedication for children [4, 22], whereas satisfactory results are seen in only 60-80% of patients [5, 25, 26]. In our study 38% of parents evaluated the anesthesia prosedure as “good” and 61% said that it was “very good”. So we can conclude that 99% of the parents were satisfied from the anesthesia prosedure. On the other hand, 13% of the surgeons’ evaluation was “good” and 87% of them said that it was “very good”. So 100% of surgeons evaluated ketamine premedication as satisfactory.

We conclude that contrary to traditional approaches, oral ketamine administration is a safe, affective, rapid and easy way of premedication for children undergoing ophthalmic surgery. It prevents preoperative anxiety and decreases anesthetic requirement with unsignificant side effects.

Disclosure of conflict of interest

None.

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References

[1] Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med 1996; 150: 1238-45.
[2] Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, Feng R, Zhang H. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004; 99: 1648-54, table of contents.
[3] McCann ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesth Analg 2001; 93: 98-105.
[4] Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. Paediatr Anaesth 2002; 12: 685-9.
[5] Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth 2000; 84: 335-40.
[6] Gharde P, Chauhan S, Kiran U. Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. Ann Card Anaesth 2006; 9: 25-30.
[7] Slogoff S, Allen GW, Wessels JV, Cheney DH. Clinical experience with subanesthetic ketamine. Anesth Analg 1974; 53: 354-8.
[8] Filatov SM, Baer GA, Rorarius MG, Oikkonen M. Efficacy and safety of premedication with oral ketamine for day-case adenoidectomy compared with rectal diazepam/diclofenac and EMLA. Acta Anaesthesiol Scand 2000; 44: 118-24.
[9] Bunch TJ, Tian B, Seeman JL, Gabelt BT, Lin TL, Kaufman PL. Effect of daily prolonged ketamine anesthesia on intraocular pressure in monkeys. Curr Eye Res 2008; 33: 946-53.
[10] Yoshikawa K, Murai Y. The effect of ketamine on intraocular pressure in children. Anesth Analg 1971; 50: 199-202.
[11] Ausinsch B, Rayburn RL, Munson ES, Levy NS. Ketamine and intraocular pressure in children. Anesth Analg 1976; 55: 773-5.
[12] Norbury A, Rocke AD, Brock-Utne JG, Mackenzie R, Welsh N, Downing JW. Balanced total intravenous anaesthesia and intraocular pressure. Anaesth Intensive Care 1981; 9: 255-9.
[13] Cugini U, Lanzetta P, Nadbath P, Menchini U. Sedation with ketamine during cataract surgery. J Cataract Refract Surg 1997; 23: 784-6.
[14] Frey K, Sukhani R, Pawlowski J, Pappas AL, Mikat-Stevens M, Slogoff S. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes, and recovery profiles. Anesth Analg 1999; 89: 317-21.
[15] Becker R, Schmidt W, Viehl H, Rupp D. [Drugs for supplementation in cataract surgery with a laryngeal mask]. Ophthalmologe 2002; 99: 752-5.
[16] Blumberg D, Congdon N, Jampel H, Gilbert D, Elliott R, Rivers R, Munoz B, Quigley H. The effects of sevoflurane and ketamine on intraocular pressure in children during examination under anesthesia. Am J Ophthalmol 2007; 143: 494-9.
[17] Jones L, Sung V, Lascaratos G, Nagi H, Holder R. Intraocular pressures after ketamine and sevoflurane in children with glaucoma undergoing examination under anaesthesia. Br J Ophthalmol 2010; 94: 33-5.
[18] Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Am J Crit Care 2010; 19: 55-61; quiz 2.
[19] Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics 2006; 118: 651-8.
[20] Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg 1999; 88: 1042-7.
[21] Watson AT, Visram A. Children's preoperative anxiety and postoperative behaviour. Paediatr Anaesth 2003; 13: 188-204.
[22] Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: a status report. Anesth Analg 1997; 84: 427-32.
[23] Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine: an alternative to benzodiazepines for premedication in children. Curr Opin Anaesthesiol 2005; 18: 608-13.

[24] Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand 2006; 50: 135-43.
[25] McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. Can J Anaesth 1992; 39: 545-50.
[26] Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. Paediatr Anaesth 1995; 5: 293-5.
[27] Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery systems with assessment of intra-observer variability. Br J Anaesth 1998; 81: 865-9.
[28] Neuhauser C, Wagner B, Heckmann M, Weigand MA, Zimmer KP. Analgesia and sedation for painful interventions in children and adolescents. Dtsch Arztebl Int 2010; 107: 241-7, I-II, I.
[29] Wolff K, Winstock AR. Ketamine: from medicine to misuse. CNS Drugs 2006; 20: 199-218.
[30] J. Schuttler EZ, PF. White. Textbook of Intravenous Anesthesia. In: White P, editor. Pennsylvania: Williams & Wilkins; 1997.
[31] Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. Anesthesiology 1992; 76: 28-33.
[32] Audenaert SM, Wagner Y, Montgomery CL, Lock RL, Colclough G, Kuhn RJ, Johnson GL, Pedigo NW Jr. Cardiorespiratory effects of premedication for children. Anesth Analg 1995; 80: 506-10.
[33] Aun CS. New i.v. agents. Br J Anaesth 1999; 83: 29-41.
[34] Spotoft H, Korshin JD, Sorensen MB, Skovsted P. The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. Can Anaesth Soc J 1979; 26: 463-7.
[35] Berman W Jr, Fripp RR, Rubler M, Alderete L. Hemodynamic effects of ketamine in children undergoing cardiac catheterization. Pediatr Cardiol 1990; 11: 72-6.
[36] Williams GD, Philip BM, Chu LF, Boltz MG, Kamra K, Terwey H, Hammer GB, Perry SB, Feinstein JA, Ramamoorthy C. Ketamine does not increase pulmonary vascular resistance in children with pulmonary hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. Anesth Analg 2007; 105: 1578-84, table of contents.
[37] Shulman D, Beardsmore CS, Aronson HB, Godfrey S. The effect of ketamine on the functional residual capacity in young children. Anesthesiology 1985; 62: 551-6.
[38] Gibbs JM. The effect of intravenous ketamine on cerebrospinal fluid pressure. Br J Anaesth 1972; 44: 1298-302.
[39] Gardner AE, Dannemiller FJ, Dean D. Intracranial cerebrospinal fluid pressure in man during ketamine anesthesia. Anesth Analg 1972; 51: 741-5.
[40] Shaprio HM, Wyte SR, Harris AB. Ketamine anaesthesia in patients with intracranial pathology. Br J Anaesth 1972; 44: 1200-4.
[41] Kolenda H, Gremmelt A, Rading S, Braun U, Markakis E. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta Neurochir (Wien) 1996; 138: 1193-9.
[42] Bourgoin A, Albanese J, Leone M, Sampol-Manos E, Viviand X, Martin C. Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. Crit Care Med 2005; 33: 1109-13.
[43] Schmittner MD, Vajkoczy SL, Horn P, Bertsch T, Quintel M, Vajkoczy P, Muench E. Effects of fentanyl and S(+)-ketamine on cerebral hemodynamics, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies: a pilot study. J Neurosurg Anesthesiol 2007; 19: 257-62.
[44] Filanovsky Y, Miller P, Kao J. Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury. CJEM 2010; 12: 154-7.
[45] Adams HA, Werner C. [From the racemate to the eutomer: (S)-ketamine. Renaissance of a substance?]. Anaesthesist 1997; 46: 1026-42.