Research Article

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Propofol versus 4-hydroxybutyric acid in pediatric cardiac catheterizations

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Abstract: Introduction: Pediatric patients require deep sedation at least for cardiac catheterizations (CCs). Usually, we perform these CCs applying propofol, but we have seen several side effects of this sedative. We have had good experience with 4-hydroxybutyric acid for other sedations. To optimize our standardized CC procedure, we initiated a prospective, randomized trial to compare the two substances.

Methods: We analyzed our sedation protocols of all CCs within a period of 12 months. In addition to the primary endpoints, the feasibility of the CCs and the occurrence of severe complications, several other parameters were included in the analysis (vital parameters, blood gas analysis, intervention measures). The protocols were blinded for the first part of the evaluation.

Results: During the 12-month-period, 36 patients were included in each group. The propofol group showed lower blood pressure values towards the end of the sedations, while the blood gas analyses revealed lower pH levels and higher pCO2 values. The complication rate was low in both groups.

Conclusion: Both procedures are suited for the safe performance of deep sedations for CCs. The application of 4-hydroxybutyric acid seems to have a few advantages with regard to spontaneous breathing, gas exchange, stability of cardiocirculatory parameters and sedation quality.

Keywords: Propofol; 4-hydroxybutyric acid; Deep sedation; Cardiac catheter; Pediatric patients

1 Introduction

In the majority of cases, pediatric patients require deep sedation or general anesthesia for diagnostic or interventional cardiac catheterizations (CCs). In line with an in-house standard, we usually perform these CCs in deep sedation, maintaining spontaneous breathing. For several years now, we have achieved good results with the application of propofol for CCs. However, we have seen several complications, predominantly relating to respiratory (e. g. desaturation, upper airway obstruction) and cardiovascular issues (e. g. hypotension, bradycardia, instability in patients with left or right-sided obstructions). On the other hand, we have had positive experience with 4-hydroxybutyric acid (4HBA) for other deep sedations, gaining the impression that particularly infants and young children were more stable in respiratory and cardiovascular terms when 4HBA was used. In a detailed review of the literature, we tried to find results and practical experience with the use of propofol and 4-hydroxybutyric acid in pediatric patients. While we found quite a few and rather contrary publications about the use of propofol, there were only few articles about 4-hydroxybutyric acid in pediatric patients in medical journals [1-4]. Both drugs are known for their effects via the GABA-receptor. Propofol acts as an agonist via the GABA-A-receptor in the CNS and as an antagonist on nicotinic acetylcholine receptors [5]. Propofol is known for its antiemetic effects as well, which is attributed to effects via serotonin receptors [5]. 4-hydroxybutyric acid is a neurotransmitter and a catabolite of GABA. It acts by connecting with the GABA-receptor. Poeschl et al emphasize that the function of 4HBA in CNS has not been fully understood yet[4]. They described actions as a major CNS

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inhibitory transmitter, effects via the GABA-B-receptor and putative GHB-receptors, inhibition of dopaminergic neurons and dopamine release as well [4]. There might also be interaction with "serotoninergic sites, thalamic NMDA and opiate receptors" [4]. For the afore-mentioned reasons, we designed a randomized, prospective study to evaluate potential advantages or disadvantages of propofol or 4-hydroxybutyric acid, in view of our positive experience with the two substances. The study was intended to focus primarily on the feasibility of CCs and the occurrence of severe complications. These were defined as complications requiring intervention, e.g. the application of drugs (particularly substances having cardio circulatory effects), administration of a bolus of balanced electrolyte solution in addition to the running infusion, mask ventilation, maintaining the airway by placing a Guedel or Wendl tube, intubation or resuscitation. We defined various parameters as secondary endpoints of the study: the occurrence of minor or medium complications (classification according to Sauer et al [6]) including changes in cardio circulatory parameters and oxygen saturations (transcutaneous determination), laboratory parameters at the end of the CC and the occurrence of complications during the post-sedative monitoring period (including nausea and vomiting).

We created a study protocol and requested the ethics committee of the Medical Association of Saarland to assess the trial. Subsequently, the corresponding author presented the project to the ethics committee. Following a renewed assessment, the ethics committee approved and registered the trial, ID 44/11. In addition the study was registered in the German Clinical Trials Register, DRK S00005262.

2 Material and methods

We analyzed the data documented in a standardized procedure (see Sauer et al [6, 7]) in our sedation protocols covering all the CCs performed at the Clinic for Pediatric Cardiology (University Hopsital of Saarland) in a 12-month-period. In this process, we took into account the following inclusion and exclusion criteria.

Inclusion criteria

- patients aged between 1 month minimum and 18 years maximum requiring a diagnostic and/or interventional CC
- parents and patient (if older than 12 years) had given the informed consent to participate in the trial

Exclusion criteria

- denial of consent by parents or custodians/legal representative(s)
- infectious disease at the time of CC or one week before
- known allergy or intolerance of one of the active substances applied
- malformations of the airways and/or other diseases which are likely to trigger complications of the airways during the anlgosedation and/or require intubation to secure the airways
- pregnancy

The standardized procedure includes an up-to-date anamnesis one day before the CC, physical examination, placement of a peripheral intravenous catheter including a blood sample to determine the laboratory parameters (such as blood count, differential blood count, electrolytes, CrP, coagulation parameters) and a detailed patient information. The randomization was carried out on the day before CC. Taking into account the recommended fasting period [6-9], the patients were connected to standard monitoring immediately before the CC (automated non-invasive measurement of blood pressure (niBP), ECG, pulse oximetry) [6, 7]. Subsequently, the patients were administered iv (intravenous) midazolam titrated by effect at a dosage of 0.1 – 0.25 mg/kg bw (body weight) to the maximum amount of 10.0 mg.

For the purpose of the subsequent sedation, one of the patient groups received propofol at an initial dosage of 10 mg/kg bw/h and boli titrated by effect, as necessary, to achieve a deep sedation level (classification according to [6-8]) – up to a maximum dosage of 2.0 mg/kg bw in total. The other group of patients was administered 4-hydroxybutyric acid at an initial dosage of 50 mg/kg bw/h and boli titrated by effect as necessary (see propofol group) at a maximum dosage of 50 mg/kg bw. When a deep sedation level was reached, 1 % lidocaine was used for local anesthesia in the groin where the cardiac catheter was to be inserted. In the course of the CC, we reduced the dosage of the propofol group by 1 mg/kg bw/h at 5 to 10-minute intervals until we reached the planned maintenance dose of 5 mg/kg bw/h. At the same time intervals, the dosage was reduced by 5 – 10 mg/kg bw/h in the 4-hydroxybutyric acid group until the planned maintenance dose of 25 mg/kg bw/h was reached. Table 1 provides a brief overview of the methods applied in the two groups.

Only those patients whose initial saturation was lower than 85 % were administered O_2 by means of nasal prongs as a prophylactic measure. In all the other patients, we did without any oxygen application.

We continually performed the aforementioned standard monitoring and documented it in a sedation protocol at intervals of 5 minutes. Before the termination of the administration of sedatives at the end of the catheterization, an extended blood gas analysis was carried out in the form of an arterial or venous collection of a blood sample depending on the vascular access (preferably arterial). Table 2 summarizes the parameters that were used for the comparison of the two groups during the analgosedation (AS). During the recovery period, the patients were monitored continually (ECG + pulse oximetry), and the niBP was measured at intervals of 15-30 minutes.

First of all, the name, the date of birth and the applied sedatives were blinded so a medical assistant could evaluate the protocols. In a second step, the protocols were unblinded again so the doses of the administered drugs could be documented. The collected data was subsequently evaluated using the IBM SSPS Statistics 20.0.0 program, taking into account the usual statistical methods (see "Results" for further details).

Table 1: Overview of the standardized procedure in the two trial groups

	Propofol group (PGr)	**4-hydroxybutyric acid group (4HGr)**
Midazolam dose	0.1 – 0.25 mg/kg bw max. 10.0 mg	0.1 – 0.25 mg/kg bw max. 10.0 mg
Initial dose via perfusor	10 mg/kg bw/h	50 mg/kg bw/h
Boli administered during induction of sedation	- 0.1 – 0.5 mg/kg bw every 60 sec - absolutely 2.5 – 20 mg - max. cumulative dose: 2 mg/bw	- 1 – 2 mg/kg bw every 30 – 60 sec - max. cumulative dose: 50 mg/kg
Reduction every 5 – 10 min by	1 mg/kg bw/h	5 – 10 mg/kg bw/h
Maintenance dose	5 mg/kg bw/h	25 mg/kg bw/h
Additional boli administered as necessary in the course of the sedation	- 0.1 – 0.5 mg/kg bw - absolutely 2.5 – 10 mg - max. cumulative dose: 2 mg/bw	- 1 – 2 mg/kg bw - max. cumulative dose: 20 mg/kg
End of sedation	Disconnection of the perfusor after drawing the CC sheath and applying a pressure bandage	

Table 2: Parameters for the comparison of the two groups

niBP (systolic and diastolic)	bS: before the start of analgosedation (AS) 10m: 10 min after start of the AS aT: 5 min after termination of the infusion of sedatives
Heart rate (HR)	bS: before the start of AS 10m: 10 min after start of the AS aT: 5 min after termination of the infusion of sedatives
Periphal oxygen saturation (pS)	bS: before the start of AS 10m: 10 min after start of the AS aT: 5 min after termination of the infusion of sedatives
Oxygen administration (by means nasal prongs or a mask)	owing to decreases in saturation by more than 10 % from the initial value or to below 90 % in absolute terms (except for patients with cyanosis even before the start of the AS or O2 administration for diagnostic reasons)
Blood gas analysis (immediately before termination of the supply of sedatives)	pH BE pCO2 lactate

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

3 Results

Taking account of the inclusion and exclusion criteria, a total of 72 patients joined our trial in the 12-month period. Table 3 provides an overview of the patients' basic data, the distribution in the two trial groups and the midazolam dose for the induction and the duration of the sedation .

Neither the entire collective nor the analysis of the subgroup of patients ≤ 24 months of age showed any significant differences in terms of the basic data listed in Table 3. In most cases, the drug dosages mentioned in Table 1 were adhered to. It was only in the 4-hydroxybutyric acid group (4HGr) that two patients received 0.252 and 0.266 mg/kg bw midazolam because the doses were rounded up. In addition, the planned maximum cumulative induction dose of 50 mg/kg bw, which is also recommended by the supplier for sedations using 4-hydroxybutyric acid, was exceeded in two cases (66.12 and 53.76 mg/kg bw). In both cases, however, these doses markedly remained below the induction dose of up to 90 mg/kg bw. Table 4 shows the administered dosages in the two groups.

Table 5 lists the results of the aforementioned parameters of Table 2. As far as the recorded values for blood pressure are concerned, it was only the value 5 min after the termination of the supply of sedatives that significant variations were recorded. The sub-group analysis for the patients ≤ 24 months (M) revealed significant variations only for the diastolic blood pressure 5 min after the termination of the supply of sedatives. In addition, it showed a trend for the base excess (BE). In the patients ≤ 24 months, it was only the pCO_2 values that showed significant differences. In the propofol group, 3 blood gas analyses could not be performed.

In line with earlier publications [6], we considered the changes in the vital parameters to be complications whenever we recorded decreases in saturation to less than 90 % or by more than 10 % from the initial value as well as variations in heart rate and blood pressure (separate assessment of systolic and diastolic BP) by more than 20 % from the initial value. In addition, events that required inter-

Table 3: Basic data of patients and analgosedations

		Propofol	4-hydroxybutyric acid	Significance (Significance level p < 0.05)
n		36	36	
Age at time of catheterization [years]		6.28 ± 4.77 min 0.08 max 16.42	5.06 ± 5.06 min 0.17 max 14.92	p = 0.217 a
Sex M = male; F = female		M: 16 (44.4 %] F: 20 (55.6 %)	M: 13 (36.1 %) F: 23 (63.9 %)	p = 0.631 b
Weight [kg]		23 ± 15 min 4; max 59	21 ± 18 min 4; max 75	p = 0.209 a
ASA class.	ASA I	8/36 (22.2 %)	9/36 (25.0 %)	p = 0.720 b
	ASA II	17/36 (47.2 %)	13/36 (36.1 %)	
	ASA III	11/36 (30.6 %)	13/36 (36.1 %)	
	ASA IV	0 (0 %)	1/36 (2.8 %)	
Midazolam [mg]		3.3 ±1,9	3.5 ± 2.7	p = 0.746 c
Duration of sedation [min]		97 ± 33	92 ± 28	p = 0.740 a

Legend table 3:
min = minimum; max = maximum; min (in context with duration of sedation) = minutes
AV = average; SD = standard deviation
Results in Propofol or 4-hydroxybutyric acid column as AV ± SD
Statistical tests: [a] Mann-Whitney U test, [b] Exact test according to Fisher
[c] Mann-Whitney U test for independent samples

Table 4: Dosages and findings in the two groups

	Propofol **1) n = 36** ***2) n = 9 (≤ 24 months)***	**4-hydroxybutyric acid** **1) n = 36** ***2) n = 16 (≤ 24 months)***
Induction dose [mg]	16 ± 9 min 2.5, max 40 *9.4 ± 5.8* *min 2.5, max 15*	611 ± 420 min 120, max 1920 *315 ± 160* *min 120, max 720*
Induction dose [mg/kg bw]	0.84 ± 0.42 min 0.17, max 1.90 *1.13 ± 0.51* *min 0.52, max 1.90*	36.28 ± 15.88 min 2.7, max 66.12 *39.47 ± 17.10* *min 17.96, max 53.76*
Maintenance dose [mg/kg bw/h]	5.88 ± 1.07 min 3.37, max 7.89 *5.57 ± 1.15* *min 3.37, max 7.75*	31.15 ± 4.53 min 24.83, max 48.0 *31.83 ± 5.34* *min 25.56, max 48.0*
Additional boli in the course of the sedation	13 out of 36 patients *5 out of 9 patients*	5 out of 36 patients *2 out of 16 patients*

Legend table 4:
Induction dose = administration of boli in addition in addition to the initial dose via perfusor as described in table 1
AV = average; SD = standard deviation; min = minimum; max = maximum
bw = body weight
Results in Propofol or 4-hydroxybutyric acid column as AV ± SD

vention during the cardiac catheterization were regarded as complications.

As far as the documented vital parameters are concerned, 5 complications in the propofol group were related to saturation (lowest saturation 72 %), 32 to heart rate (none of the patients required any parasympatholytic agents, in particular atropine or beta-sympathomimetics to increase the heart rate) and 14 to blood pressure. In the 4-hydroxybutyric acid group, 3 complications related to saturation (lowest saturation 58 %), 28 to heart rate (no medication required, as was the case before) and 26 to blood pressure. It was only in blood pressure (exact test according to Fisher two-sided significance) that there was a significant difference (p = 0.009). Apart from volume loading (crystalloid solution) in addition to the running basic infusion (= fulfillment of the calculated maintenance dose), no other measures were necessary. In the propofol group, 2 patients required the following interventions in addition to the oxygen administration:

- Pat. 1: suction of remaining secretion; insertion of a Guedel tube
- Pat. 2: jaw thrust maneuver; insertion of a Wendl tube

In the 4-hydroxybutyric acid group, there were also 2 patients who required additional interventions apart from oxygen administration:

- Pat. 1: suction of remaining secretion, xylometazolin nose drops due to nosebleed after suction maneuver
- Pat. 2: repeated suction of remaining secretion and vomiting (three times); insertion of a Wendl tube; the patient, who suffers from adipositas per magna, admitted in the evening that she had eaten a bar of chocolate and drunk 250 mL of fruit juice immediately before the catheterization.

The sub-group analysis for the patients ≤ 24 months did not reveal any significant variations with regard to the vital parameters.

Unfortunately, the analysis of the sedation protocols does not provide any information about the reasons for additional volume boli: Were they given because of the hypotension as a result of the sedation or because of difficult puncture conditions in the groin and supposed hypovolemia? Consequently, no exact complication rate with respect to the recorded systolic and diastolic blood pressure for the purpose of one of the primary endpoints could be calculated.

Table 5: Vital parameters, blood gas analyses and oxygen administration in the two groups

	Propofol **1) n = 36** *2) n = 9 (≤ 24 M)* **AV ± SD**	**4-hydroxybutyric acid** **1) n = 36** *2) n = 16 (≤ 24 M)* **AV ± SD**	**Significance** **Significance level:** **p < 0.05**
niBP bS [mmHg]	112 ± 15 / 64 ± 14	114 ± 16 / 64 ± 9	0.652 [a] / 0.499 [a]
Systole / diastole	*103 ± 14 / 58 ± 18*	*107 ± 17 / 61 ± 7*	*0.760 [a] / 0.152 [a]*
niBP 10m	92 ± 13 / 51 ± 9	99 ± 16 / 54 ± 11	0.064 [a] / 0.116 [a]
[mmHg]	*84 ± 13 / 45 ± 11*	*91 ± 15 / 49 ± 11*	*0.229 [a] / 0.357 [a]*
Systole / diastole			
niBP aT	97 ± 15 / 55 ± 10	107 ± 18 / 60 ± 12	**0.019 [a] / 0.029 [a]**
Systole / diastole	*89 ± 12 / 46 ± 9*	*100 ± 16 / 55 ± 10*	*0.096 [a] / **0.032** [a]*
Lowest niBP [mmHg]	78 ± 9 / 41 ± 6	82 ± 10 / 42 ± 7	0.125 [a] / 0.373 [a]
Systole / diastole	*74 ± 10 / 37 ± 5*	*78 ± 10 / 40 ± 8*	*0.252 [a] / 0.276 [a]*
HR bS	106 ± 22	109 ± 20	0.543 [a]
[bpm]	*132 ± 11*	*122 ± 19*	*0.095 [a]*
HR 10m	99 ± 17	98 ± 18	0.685 [a]
[bpm]	*120 ± 14*	*106 ± 18*	*0.065 [a]*
HR aT	92 ± 16	91 ± 21	0.951 [a]
[bpm]	*111 ± 15*	*109 ± 15*	*0.978 [a]*
Lowest HR	85 ± 17	80 ± 18	0.347 [a]
[bpm]	*106 ± 11*	*95 ± 12*	0.037 [a]
pS bS	96 6	96 ± 6	0.748 [a]
[%]	*93 ± 9*	*94 ± 7*	*0.803 [a]*
pS 10m	94 ± 5	95 ± 5	0.075 [a]
[%]	*91 ± 7*	*95 ± 5*	*0.095 [a]*
pS aT	95 ± 5	96 ± 5	0.807 [a]
[%]	*93 ± 8*	*95 ± 6*	*0.803 [a]*
Lowest pS	91 ± 6	92 ± 6	0.184 [a]
[%]	*90 ± 8*	*91 ± 7*	*0.419 [a]*
O_2 administration	8 out of 36 (22.2 %)	6 out of 36 (16.7 %)	0.767 [b]
	3 out of 9 (33.3 %)	*3 out of 16 (18.8 %)*	*0.630 [b]*
BGA:	28 / 5	25 / 11	0.161 [b]
arterial/ venous	*7 / 1*	*12 / 4*	*0.631 [b]*
pH	7.292 ± 0.032	7.337 ± 0.028	**< 0.001 [a]**
	7.294 ± 0.034	*7.296 ± 0.120*	*0.106 [a]*
BE [mmol/l]	- 4.4 ± 1.8	- 3.2 ± 2.8	0.073 [a]
	- 5 ± 1.5	*- 4.4 ± 2.5*	*0.834 [a]*
pCO_2 [mmHg]	46.4 ± 4.8	42.3 ± 6,7	**0.001 [a]**
	44.2 ± 3,8	*39.7 ± 7,7*	***0.011** [a]*
pCO_2 < 45 mmHg /	12 / 21	26 / 10	**0.004 [b]**
pCO_2 > 45 mmHg	*5 / 3*	*14 / 2*	*0.289 [b]*
Lactate [mmol/l]	0.84 ± 0.48	0.95 ± 0.33	**0.026 [a]**
	0.6 ± 0.2	*0.8 ± 0.3*	*0.106 [a]*

Legend table 5:bS = before the start of analgosedation (AS)

10m = 10 minutes after start of AS
aT = 5 minutes after termination of the infusion of sedatives
HR = heart rate; niBP = non-invasive blood pressure; pS = periphal oxygen saturation
AV = average; SD = standard deviation
Results in Propofol or 4-hydroxybutyric acid column as AV ± SD
Statistical tests: [a]Mann-Whitney U test of unidentical samples
[b]Exact test according to Fisher two-sided significance

Table 6: Events and measures during the recovery phase

	Propofol group	4-hydroxybutyric acid group	Significance Significance level: $p < 0.05$
Restlessness 1) n = 36 *2) n = 9 and 16 (≤ 24 M)*	13 (36.1 %) *6 (66.7 %)*	16 (44.4 %) *11 (68.8 %)*	0.631 [a] *1.0 [a]*
Administration of analgetics 1) n = 36 *2) n = 9 and 16 (≤ 24 M)*	11 (30.6 %) *0 (0 %)*	11 (30.6 %) *2 (12.5 %)*	1.0 [a] *0.520 [a]*
Administration of sedatives 1) n = 36 *2) n = 9 and 16 (≤ 24 M)*	6 (16.7 %) *2 (22.2 %)*	8 (22.2 %) *5 (31.3 %)*	0.767 [a] *1.0 [a]*
PONV 1) PGr: n = 36; 4HGr: n = 21 *2) n = 9 and 11 (≤ 24 M)* (4HGr without antiemetics)	4 (11.1 %) *0 (0 %)*	13 (61.9 %) *6 (54.5 %)*	**< 0.001 [a]** ***0.02 [a]***
PONV 1) PGr: n = 36; 4HGr: n = 15 *2) n = 9 and 5 (≤ 24 M)* (4HGr with antiemetics)	4 (11.1 %) *0 (0 %)*	3 (20 %) *0 (0 %)*	0.406 [a] *1.0 [a]*
Administration of antiemetics during recovery phase PGr: n = 36; 4HGr: n = 36	3 (8.3 %)	4 (11.1 %)	1,0 [a]
Oxygen application 1. n = 36 *2. n = 9 and 16 (≤ 24 M)*	3 (8.3 %) *1 (11.1 %)*	6 (16.7 %) *3 (18.8 %)*	0.478 [a] *1.0 [a]*

Legend table 6:
Statistical test: aExact test according to Fisher two-sided significance
M = months
PGr = Propofol group; 4HGr = 4-hydroxybutyric acid group

All the catheterizations could be performed smoothly. Overall, we had the subjective impression that the patients of the 4-hydroxybutyric acid group better tolerated the injection of the local anesthesia in the groin that was to be punctured. However, we could not objectify this retrospectively because the relevant documentation did not exist.

In the post-sedative observation period up to the complete recovery of the patients including the first intake of food we discovered some interesting aspects. The results have been summarized in Table 6.

With regard to the parameters of "restlessness" and "need to administer drugs (sedatives, analgetics and/or antiemetics)", neither the entire collective nor the subgroup analysis showed any significant variations. As far as the occurrence of post-operative nausea and vomiting (PONV) is concerned, an interim evaluation after 6 months revealed that PONV occurred far more frequently in the 4-hydroxybutyric acid group (n = 21 after 6 months) than in the propofol group. For this reason, we applied dimenhydrate to the patients of the 4HGr in the second half of the trial (n = 15). These patients received the drug in a dosage of 1 – 2 mg/kg bw about 10 minutes before the termination of the sedation to prevent PONV. This measure proved to be effective and resulted in a marked reduction of PONV from 61.9 % to 20 % in all patients and from 54.5 % to 0% in the patients ≤ 24 months. In addition, the administration of antiemetics in the recovery phase was reduced. Whereas 3 patients required antiemetics in the recovery phase (3 out of 21 patients = 14.3 %), the administration of this drug was only necessary in one patient (1 out of 15 = 6.7 %) after the application of the PONV prophylaxis.

4 Discussion

The feasibility of diagnostic and/or interventional procedures and the safety of the patients are the decisive quality criteria of deep (analgo-) sedations maintaining sponta-

neous breathing. We think that a standardized approach is indispensable – as has been stressed before [6, 7]. This assessment is reflected in the relevant guidelines and the literature [8, 10, 11]. With other publications we share the opinion that the qualification and training of the person performing and monitoring the sedation [9, 10, 12-14] and the adequate equipment of the sedation work place [14-17] plays a decisive role.

With regard to the primary endpoints it can be stated that both sedation procedures fully grant the feasibility of a diagnostic or interventional cardiac catheterization. With respect to 4HBA, this contrasts with the results by Poeschl et al, who reported a rate of 3 % of insufficient sedations using 4HBA in a subgroup of 65 pediatric patients for MRI [4] or Meyer et al who mentioned 2 out of 14 patients (= 14,3 %) with insufficient 4HBA-sedation for MRI [2]. There were rare cases of severe complications in both groups – two each (= 5.5 %). By means of the aforementioned measures, they could easily be handled and remedied. The frequency of desaturations in the two groups (PGr: 5 = 13.9 %, 4HGr: 3 = 8,3.%) was rather low. Meyer et al reported nearly the same rate of desaturation in children sedated with 4HBA for MRI (1 (= 7,1 %) in a group of 14 children) [2]. As far as propofol is concerned, the rates were in line with the well-known range of sedations with propofol (frequency of desaturations: 2 – 31 %) [18, 19]; however, they were slightly higher than described by Cravero et al for (analgo-) sedations in pediatric patients [20] and for sedations with propofol [21]. None of our patients required mask ventilation or intubation, as had been described in other papers [20-22]. In both groups, cardio circulatory stability was granted, with 32 of the recorded heart rate and 14 of the blood pressure values (systole or diastole) in the propofol group showing a deviation by more than 20 % below the initial value, whereas in the 4-hydroxybutyric acid group there were 28 and 26 of these cases respectively. A significant variation was only evident for the low blood pressure values in the propofol group towards the end of the sedation. None of our patients required parasympatholytics or catecholamines. All that was applied was volume boli in addition to the basic infusion rate. Meyer at al mentioned cardiovascular parameters under 4HBA-sedation but they report only the mean values and standard deviations of heart rates, systolic and diastolic pressures [2]. Unfortunately, they did not define any criteria for cardiovascular complications – for this reason their and our results are not comparable.

With respect to the secondary endpoints – focusing on blood gas analyses and post-sedative complications, in particular – the propofol group revealed lower ph and higher pCO_2 values. In general, the measured pCO_2 values after an average sedation duration of nearly 100 min in both groups did not significantly exceed the normal range (35 – 45 mmHg). In the historical paper by Hunter et al about 4HBA, the pCO_2 levels were a bit lower than in our patients. We have not implemented the expiratory CO_2 monitoring in our standard yet. Since in the case of hypoventilation/apnea desaturations only become evident with a delay of about 60 – 90 seconds [17], sedations for our cardiac catheterizations are only performed by experienced pediatricians (consultants, sub specialization in pediatric cardiology and intensive care) who are permanently present at the bed-side. Some papers describe and/or recommend the expiratory CO_2 monitoring [11, 16, 17, 23-26]. An investigation in sedations for adolescents and adults under room air conditions has shown that most desaturations are detected earlier by means of pulse oximetry than by changes in capnometry [27]. Although the pCO_2 values we recorded after long sedations provide only little evidence for hypoventilation, we think it is reasonable to implement capnography in our standard monitoring.

We were astonished to find significantly higher lactate values in the 4-hydroxybutyric acid group, something we would rather have expected in the propofol group. In both groups, however, the measured lactate values were in line with the norm (< 2.2 mmol/l).

As was the case in other papers [2, 28], we also noted a markedly higher PONV rate in the 4-hydroxybutyric acid group. This is not surprising given the antiemetic effect of propofol, which has been known for a long time [29, 30]. The prophylactic administration of dimenhydrinate about 10 min before the termination of the sedation allowed the occurrence of PONV to be reduced to the level of the propofol group.

The rate of additional sedation boli was higher in the propofol group (13 cases as compared to 5 in the 4-hydroxybutyric acid group). In addition, we had the subjective impression that the 4-hydroxybutyric acid group tolerated the administration of the local anesthesia in the groin better than the propofol group. This could indicate a higher sedation quality with 4-hydroxybutyric acid.

In the majority of cases, the applied drug doses were in line with the supplier recommendations in both groups. As far as propofol is concerned, the recommended induction dose for sedations in children beyond the first month of life ranges between 1 and – 2 mg/kg bw, whereas the dose for maintaining the sedation ranges from 1.5 to 9 mg/kg bw/h [31]. For 4-hydroxybutyric acid, the recommended induction dose amounts to 30 – 50 mg/kg bw, depending on the efficiency up to 90 mg/kg bw, applied for a time period of 10 min. The maintenance dose is quoted as being

10 – 20 mg/kg bw/h [31], which we consider to be rather low after many years of experience with this substance. Our trial also resulted in an average maintenance dose of just over 31 mg/kg bw/h, which is higher than in other studies [4, 28]. In line with Chidambaran et al we recommend continuous infusion for sedation with both propofol [5] and 4HBA to reduce the rate of typical complications. If a bolus is needed for the induction of the sedation, it is mandatory to administer sedatives carefully by titration according to effect.

The ongoing debate of the past few years [10, 13] about sedations and analgosedations for diagnostic and/or interventional procedures in pediatric patients in general and the application of propofol by non-anesthesiologists in particular [32] has resulted in medical and legal conflicts. By contrast, there are two studies involving large groups of patients (49,836 and 25,433), which recommend to adhere to certain conditions when applying propofol, but which conclude that this substance is rather unlikely to cause severe complications [22, 33]. As we stated at the beginning of our discussion, we think that a standardized approach is indispensable. Chidambaran et al were absolutely right stating that when performing sedations with propofol "it is important for the providers to select patients wisely" [5].

The weaknesses of our randomized prospective study include, for one thing, the low number of patients. In addition, the documentation did not reveal the administration of volume boli of a balanced electrolyte solution in case of hypotonia, which relates to one of the primary endpoints (severe complications). Other aspects such as the quality of the sedation or the tolerance of the local anesthesia, which were not focused on until the evaluation of the study, could not be assessed sufficiently. Furthermore, the duration of the recovery phase could be clinically relevant.

5 Conclusion

As a result of the trial, we can summarize that both sedation protocols ensure good sedation conditions as well as a lower rate of severe complications overall. The application of 4-hydroxybutyric acid provides some advantages with respect to sufficient spontaneous breathing, gas exchange and stability of some cardiocirculatory parameters as well as sedation quality. However, the administration of an antiemetic before the end of the sedation is highly recommended owing to the higher rate of PONV. Further investigations with larger groups of patients are required to optimize the quality of sedations maintaining spontaneous breathing in pediatric patients.

Conflict of interest: The corresponding author and the co-authors declare that there is no conflict of interests whatsoever. In particular, there are no contacts with or financial contributions from pharmaceutical companies that produce one or more of the active substances mentioned in this paper.

References

[1] Hunter A, Long W, Ryrie C. An Evaluation of Gamma-Hydroxybutyric Acid in Paediatric Practice; Brit. J. Anaesth. 1971; 43: 620-628

[2] Meyer S, Gottschling S, Georg T, Lothschuetz D, Graf N, Sitzmann F. Gamma-hydroxybutyrate Versus Chlorprothixene/Phenobarbital Sedation in Children Undergoing MRI Studies; Klin Paediatr 2003; 215: 69-73

[3] Meyer S, Kleinschmidt S, Gottschling S, Gortner L, Strittmatter M. Gamma-hydroxy butyric acid: Neurotransmitter, sedative and party drug; Wien Med Wochenschr 2005; 155/13-14: 315-322

[4] Poeschl J, Koelker S, Bast T, Bruessau J, Ruef P, Linderkamp O, Bettendorf M. Gamma-Hydroxybutyric Acid Sedation in Neonates and Children Undergoing MR Imaging; Klin Paediatr 2007; 219: 217-219

[5] Chidambaran V. Costandi A. D´Mello A. Propofol: A Review of its Role in Pediatric Anesthesia and Sedation; CNS Drugs 2015; 29(7): 543-563

[6] Sauer H, Gruenzinger L, Pfeifer J, Lieser U, Abdul-Khaliq H. Sedation and Analgosedation Performed by Pediatricians – Experience Made with the Implementation of an In-House Sedation Standard; Wien Med Wochenschr 2016; 166: 54-61

[7] Sauer H, Haase R, Lieser U, Horneff G. Preparation and monitoring of sedation and analgosedation carried out by pediatricians and pediatric training assistants; Klin Padiatr 2008; 220: 189-195

[8] American Academy of Pediatrics and the American Academy of Pediatric Dentistry (2006, Reaffirmed 2011). Guideline for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures; Pediatrics 2012; 129; e1103

[9] American Society of Anesthesiologists. Statement of granting privileges for administration of moderate sedation to practitioners who are not anesthesia professionals; Approved by the ASA House of Delegates on October 25, 2005, and last amended on October 19, 2011

[10] Gozal D, Mason K. Pediatric Sedation: A Global Challenge; Int J Pediatr. 2010; 2010: 701257

[11] Krauss B, Green S. Procedural sedation and analgesia in children; Lancet 2006; 367:766-780

[12] American Society of Anesthesiologists. Advisory on granting privileges for deep sedation to non-anesthesiologists sedation practitioners; Approved by the ASA House of Delegates on October 20, 2010

[13] Leroy P, Schipper D, Knape H. Professional Skills and Competence for Safe and Effective Procedural Sedation in Children: Recommendations Based on a Systemic Review of the Literature; Int J Pediatr. 2010; 2010: 934298
[14] Ramaiah R, Bhananker S. Pediatric procedural sedation and analgesia outside the operating room: anticipating, avoiding and managing complications; Expert Rev. Neurother. 2011; 11: 755-763
[15] American Society of Anesthesiologists. Standard for basic anesthetic monitoring; Committee of Origin: Standards and Practice Parameters; Approved by the ASA House of Delegates on October 21, 1986, and last amended on October 20, 2010 with effective date of July 1, 2011
[16] Mahajan C, Dash H. Procedural sedation and analgesia in pediatric patients; J Pediatr Neurosci. 2014; 9: 1-6
[17] Tobias J, Leder M. Procedural sedation: A review of sedative agents, monitoring, and management of complications; Saudi J Anaesth. 2011; 5: 395-410
[18] Barbi E, Gerarduzzi T, Marchetti F et al. Deep Sedation With Propofol by Nonanesthesiologists; Arch Pediatr Adolesc Med. 2003; 157: 1097-1103
[19] Mace S, Barata I, Cravero J, Dalsey WC, Godwin SA, Kennedy RM, Malley KC, Moss RL, Sacchetti AD, Warden CR, Wears RL; American College of Emergency Physicians. Clinical Policy: Evidence-Based Approach to Pharmacologic Agents Used in Pediatric Sedation and Analgesia in the Emergency Department; Ann Emerg Med. 2004; 44: 342-377
[20] Cravero J, Blike G, Beach M, Gallagher SM, Hertzog JH, Havidich JE, Gelman B; Pediatric Sedation Research Consortium. Incidence and Nature of Adverse Events During Pediatric Sedation/Anesthesia for Procedures Outside the Operating Room: Report From the Pediatric Sedation Research Consortium; Pediatrics 2006; 118: 1087-1096
[21] Cravero JP, Beach ML, Blike GT, Gallagher SM, Hertzog JH; Pediatric Sedation Research Consortium. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium; Anesth Analg 2009; 108: 795-804
[22] Mallory MD, Baxter AL, Yanosky DJ, Cravero JP. Emergency Physician-Administered Propofol Sedation: A Report on 25,433 Sedations from the Pediatric Sedation Research Consortium; Ann Emerg Med 2011; 57: 462-468
[23] Barbi E, Petaros P, Badina L , Pahor T, Giuseppin I, Biasotto E, Martelossi S, Di Leo G, Sarti A, Ventura A. Deep Sedation with Propofol for Upper Gastrointestinal Endoscopy in Children, Administered by Specially Trained Pediatricians: a Prospective Case Series with Emphasis on Side Effects; Endoscopy 2006; 38: 368-375
[24] Langhan M, Chen L, Marshall C, Santucci K. Detection of Hypoventilation by Capnography and Its Association With Hypoxia in Children Undergoing Sedation With Ketamine; Pediatr Emer Care 2011; 27: 394-397
[25] Mora Capin A, Miguez Navarro C, López López R, Maranón Pardillo R. Usefulness of capnography for monitoring sedoanalgesia: influence of oxygen on the parameters monitored; An Pediatr (Barc) 2014; 80: 41-46
[26] Waugh J, Epps C, Khodneva Y. Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis; Journal of Clinical Anesthesia 2011; 23: 189-196
[27] Sivilotti M, Messenger D, van Vlymen J, Dungey P, Murray H. A comparative evaluation of capnometry versus pulse oximetry during procedural sedation and analgesia on room air; CJEM 2010; 12: 397-404
[28] Kleinschmidt S, Schellhase C, Mertzlufft F. Continuous sedation during spinal anaesthesia: gamma-hydroxybutyrate vs. propofol; Eur J Anaesthesiol. 1999; 16: 23-30
[29] Borgeat A. Recovery from propofol and its antiemetic effect in pediatric anesthesia; Cah Anesthesiol. 1993; 41: 231-234
[30] Soppitt A, Glass P, Howell S, Weatherwax K, Gan T. The use of propofol for its antiemetic effect: a survey of clinical practice in the United States; J Clin Anesth. 2000; 12: 265-269
[31] Rote Liste: Drug information for Germany (including EU drug licensing and certain medical products), online version 2019; information about propofol and 4-Hydroxybutyric acid (gamma-Hydroxybutyric acid)
[32] Perel A. Non-anaesthesiologists should not be allowed to administer propofol for procedural sedation: a Consensus Statement of 21 European National Societies of Anaesthesia; Eur J Anaesthesiol 2011; 28: 580-584
[33] American Society of Anesthesiologists. Advisory on granting privileges for deep sedation to non-anesthesiologists sedation practitioners; Approved by the ASA House of Delegates on October 20, 2010