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a) What is already known?

Total Intravenous Anesthesia (TIVA) is used in less than 10% of anesthetics in the UK. Some of the barriers to TIVA use include lack of detailed knowledge about the technique, lack of availability of specific TIVA pumps and having to make up infusions and programme pumps prior to administration. Up to 38% of surveyed Pediatric Anesthetists in the UK and Ireland use mixtures of propofol and remifentanil in a single syringe to simplify the process. Currently, they are using an unlicensed product, which some claim has a number of disadvantages over separate infusions. Very little has been published on the safety profile and effectiveness of this technique.

b) What this article adds?

This service evaluation demonstrates that effective TIVA can be administered to pediatric patients using various concentrations of propofol and remifentanil, with a low incidence of adverse effects. The adverse effects are generally predictable from the properties of the drugs being administered and the incidence of serious complications, such as laryngospasm, is lower than reported in other studies, including APRICOT. No life-threatening adverse effects occurred as a result of the mixture being administered for anesthesia. Lower concentrations of remifentanil in the mixture are associated with fewer complications.

Abstract

Background: Total Intravenous Anesthesia is used in less than 10% of operations in the UK. Many pediatric anesthetists in the UK and Ireland administer Total Intravenous Anesthesia to children using a mixture of propofol and remifentanil in the same syringe. This unlicensed drug has not been studied clinically, because of lack of Medicines and Healthcare products Regulatory Agency (UK) or Food and Drug Administration (US) approval to undertake such studies.

Aim: The aim of this service evaluation was to assess the safety profile and effectiveness of propofol-remifentanil mixtures in the pediatric population undergoing a variety of surgical procedures.

Methods: Pediatric Anesthetists in the UK and Ireland who regularly used propofol-remifentanil mixtures for Total Intravenous Anesthesia were invited to submit data. This data was analysed to assess the effectiveness of anaesthesia and the incidence and nature of any complications that occurred.

Results: Usable data was collected from 873 patients. Mixtures were most commonly administered in Gastroenterology and Ear Nose and Throat procedures. Two-thirds of patients were less than 10 years old and their mean weight was 28.7 kg. Anesthesia using the mixture alone was successful in all but 3 patients. The commonest non-serious complication was coughing (4.6%), followed by movement (3.3%). The overall incidence of serious, related, unexpected adverse events requiring intervention was 1.7%. These included desaturation (5 patients), apnea (3), abdominal/chest rigidity (2), cough requiring paralysis (2), ventilatory problems (2), and hypotension (1). Most occurred at induction, were attributable to the properties of the drugs being administered and not directly related to the use of the mixture. No life-threatening adverse events were recorded. Complications were less common if a ≤5 $\mu g.ml^{-1}$ concentration of remifentanil was used.

Conclusion: These data demonstrate that effective anesthesia can be administered to pediatric patients undergoing a wide range of procedures using mixtures of propofol and remifentanil. Serious, related, unexpected adverse events requiring intervention had a low incidence and were largely due to predictable effects of the drugs being administered. A ≤5 $\mu g.ml^{-1}$ remifentanil concentration is associated with proportionately less complications.

Keywords: Intravenous anesthesia; propofol; remifentanil; pediatric; complications

Introduction

Total Intravenous Anesthesia (TIVA) is used as an alternative to volatile anesthesia in a number of situations in children, including anesthesia outside the operating theater, high risk of postoperative nausea and vomiting, spinal surgery and patients with a family history of malignant hyperthermia. It is also the preferred technique of some anesthetists, although it is currently used for less than 10% of cases in the UK and Ireland[1,2].

The most popular method of TIVA administration in the UK and Ireland in children is with propofol and remifentanil[3]. Traditionally, these have been administered as separate infusions, but in recent years the use of mixtures of propofol and remifentanil has become increasingly popular. A recent survey of Pediatric Anesthetists in the UK and Ireland showed that 24% of respondents used mixtures frequently or all the time, with another 14% using them occasionally[3]. Although propofol is licensed to be mixed with both alfentanil and lidocaine[4], this is not the case for remifentanil. Studies have suggested that the mixture is unstable and causes layering of the drugs[5,6], although these studies had limitations, due to their design and the measured remifentanil concentrations[7].

In reality, there are many anesthetists in the UK and Ireland who are using mixtures of propofol and remifentanil and have done so for a number of years, but there is very little data from clinical studies to support their use with respect to safety profile and effectiveness. Members of the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) TIVA Interest Group undertook a service evaluation of mixture-based anesthesia, by collecting data from pediatric patients, to demonstrate that the incidence and severity of complications was similar to volatile-based techniques.

Methods

All anesthetists within the APAGBI TIVA Interest Group, who participated, were requested to submit data about the anesthetic management and perioperative complications of a convenience sample of patients in whom a propofol-remifentanil mixture was used. Anesthetists were encouraged to enter all their cases during the evaluation period. Data was collected on a combination of an Excel spreadsheet held locally and directly into a secure Survey Monkey (Survey Monkey, San Mateo, California, USA) account owned by the Birmingham Children's Hospital Anaesthetic Department, using a QR reader code. Specific questions were asked regarding the patient, procedure and anesthetic technique used. Data was also collected on complications throughout anesthesia and into the recovery period. No patient identifiable data was collected, although personal data such as date of birth, weight and type of surgery was recorded and held locally. Each participating centre was responsible for collecting and storing their own patient data, if it was not entered directly into the Survey Monkey account. Collection was continued for a 6-month period, with the aim of obtaining data from between 500 and 1000 patients.

There were strict definitions in place to record complications accurately. Complications were graded as serious if they required intervention to prevent significant patient morbidity. All other complications were regarded as non-serious, irrespective of whether or not intervention was required.

Given that this was a prospective evaluation of a well-established anesthetic technique involving routine patient care, it is felt that there were no ethical concerns relating to the review. Birmingham Children's Hospital Research and Development Department confirmed that Ethics approval would not be required. Subsequently, each centre secured their own Research & Development and/or Caldicott Guardian approval to undertake the evaluation prior to the collection of data.

Analysis

Routine data analysis and reporting was undertaken. Currently, there are several published studies of the incidence of complications in children, so we undertook a comparison between the results of this service evaluation and those previous studies, including the recent APRICOT study[8-12].

Complications were reviewed by three of the authors independently (OB, PB and JM) to determine which could be graded as serious, related and unexpected. Only those requiring intervention by the anesthetist were examined further. Where there was disagreement, further negotiation was undertaken until all three authors agreed on the final list.

Data are mainly presented as proportions for demographic and complication data, and median and interquartile range for pharmacological data. As there were small numbers of patients receiving the 2.5 $\mu g.ml^{-1}$ and 20 $\mu g.ml^{-1}$ remifentanil concentrations, these were combined with the 5 $\mu g.ml^{-1}$ and 10 $\mu g.ml^{-1}$ groups respectively; to make two main groups of ≤ 5 $\mu g.ml^{-1}$ and ≥ 10 $\mu g.ml^{-1}$. Given that this was a representative sample of interest, rather than a truly random sample of patients, we decided to undertake limited statistical analysis. Analysis was undertaken with SPSS statistical software and the Chi-square value calculated for the remifentanil concentration and the occurrence of complications.

Results

Demographic data

Data was collected on a total of 880 patients. Seven records were incomplete and could not be analysed, leaving 873 patients. Two-thirds of patients were under the age of 10 years, with a range of 13 days to 18.5 years. The mean weight was 28.7 kg (range 2.0-97 kg). Most (88%) were ASA 1 and 2. Other demographic data is presented in Table 1. Gastroenterology was the most common surgical specialty (20.7%), followed by Ear Nose and Throat (20.6%) and Dental/Maxillofacial Surgery (15%). In total, 16 specialties were represented (Table 2).

In nearly 90% of patients, TIVA was used as anesthetist's preference, rather than for a specific indication.

The next commonest reason was a history of postoperative nausea and vomiting in 5.5% of patients. A family history of malignant hyperpyrexia was recorded in 6 patients.

Anesthesia

Less than 11% of patients received premedication. Of those that did, just over half received analgesic premedication alone and the remainder sedative premedication. Midazolam alone was used in half the patients, with clonidine alone or in combination with midazolam, used in most of the rest. Intravenous induction of anesthesia was favored in two-thirds of patients, with the remainder receiving a gaseous induction.

Propofol 1% in combination with remifentanil 5 $\mu g.ml^{-1}$ (PR5), or the equivalent with 2% propofol, was used in 78.6% of cases. The other combinations documented were PR10 (14%), PR20 (5.8%) and PR2.5 (1.5%). The Paedfusor model was used for propofol administration in over 97% of patients, with the Marsh adult and Schnider models used in the remainder. There were 55 patients heavier than 61 kg, the maximum weight the Paedfusor model will allow to be programmed. Of those, 41 were anesthetised using Paedfusor, with weights ranging from 64 to 89 kg. The majority had bowel endoscopy procedures, but there were also several who had Ear Nose and Throat, Dental and Orthopaedic procedures. There were 10 patients below 5 kg in weight, the minimum programmable weight for Paedfusor, who received propofol TCI using the model. Nearly all of them were having airway endoscopy procedures.

Table 3 gives information about the propofol target concentrations used during anesthesia. Remifentanil infusion rates were not calculated intraoperatively until the end of anesthesia. The median overall remifentanil dose administered was 0.17 $\mu g.kg^{-1}.min^{-1}$ (range 0.01-0.89 $\mu g.kg^{-1}.min^{-1}$), calculated from total remifentanil dose.kg^{-1} and duration of anesthesia. The median end-remifentanil dose was 0.09 $\mu g.kg^{-1}.min^{-1}$ (range 0.01-0.63 $\mu g.kg^{-1}.min^{-1}$; IQR 0.04). This reflects the preponderance of PR5 use in surgery. Figure 1 shows the estimated end-remifentanil infusion rate for different remifentanil concentrations, based on the available data.

The airway was maintained with a supraglottic airway device (46.6%), an endotracheal tube (26.3%) or a non-invasive technique such as nasal cannulae or Optiflow® in the remainder. Most patients receiving ≥PR10 (94%) required full mechanical ventilation. The ≤PR5 patients managed to maintain spontaneous ventilation in 82% of cases, although 20% of those received some form of positive-pressure ventilation, such as pressure-support.

Only 35 (4%) patients received an initial dose of neuromuscular blocking drug (NMBD) and of those, only 9

received a further dose intraoperatively for maintenance purposes. Neuromuscular blocking drugs were used for intubation in 15.2% of patients who received an endotracheal tube. Rocuronium (88%) was used more frequently than atracurium (12%). If NMBDs were used, only 7% of patients required reversal at the end of the procedure.

The procedure was completed with TIVA in all patients and only three patients required a period of supplementation with volatile anesthesia; one for an inadequate local anesthetic block, one for persistent coughing on the supraglottic airway, and one for reasons that were unclear. The median duration of propofol-remifentanil administration was 32 minutes. Most procedures (84.7%) lasted less than 60 minutes, but in 3.4% the duration was greater than 2 hours in length. The longest procedure was 334 minutes.

Complications

A total of 224 complications were reported during 159 anesthetics (18.2%). More than one complication occurred in 36 patients. Induction, intraoperative and recovery complications occurred in 9.6%, 7.6% and 5.5% of patients respectively. The commonest non-serious complication was coughing, which occurred in 40 (4.6%) patients, mainly on induction. Patient movement was the next commonest non-serious complication, occurring in 3.3% of patients and requiring intervention in 93% of cases.

Laryngospasm occurred in two patients during gaseous induction prior to the commencement of TIVA, but neither required intervention. Table 4 shows a summary of all complications that occurred during the perioperative period and the proportion requiring intervention.

The incidence of serious, related, unexpected adverse events requiring intervention was 1.7% of all procedures. The most frequent were desaturation (5 patients) and apnea (3 patients). Table 5 lists the individual events. None of these were deemed life threatening. Analysis showed that the incidence of these complications in the ≥10 $\mu g.ml^{-1}$ group was higher than expected (Pearson's Chi-squared 15.7; $p<0.0001$).

No significant complications occurred in the small group of patients who received the 2.5 $mcg.ml^{-1}$ remifentanil concentration, but were present in all other groups. Proportionately, fewer overall complications occurred with the remifentanil ≤5 $\mu g.ml^{-1}$ concentration than the ≥10 $\mu g.ml^{-1}$ concentration (Pearson's Chi-squared 64.4; $p<0.0001$). Table 2 indicates the differing proportion of complications between the ≤5 $\mu g.ml^{-1}$ concentration and the ≥10 $\mu g.ml^{-1}$ concentration for each specialty. In all but one specialty, the ≤5 $\mu g.ml^{-1}$ concentration had fewer complications. Table 6 shows the overall incidence of

complications related to the concentration of remifentanil used.

Induction adjuncts in the form of lidocaine, propofol and remifentanil boluses administered separately by hand were used in 20.5% of patients. These were associated with a proportionately higher incidence of induction complications, such as cough, desaturation, apnoea, bradycardia and chest rigidity.

Discussion

Propofol-remifentanil, single-syringe mixture has become a popular way of administering TIVA in children in the UK and Ireland. A recent survey showed that 38% of respondents used mixtures[3]. This technique is convenient, requires only one TCI pump for administration, and can be used in a wide variety of patients and procedures. Despite a limited number of studies supporting the use of mixtures in specific clinical situations[13-16], there has never been an extensive examination of the safety profile and effectiveness of the technique in pediatric patients. Our aim was to undertake a service evaluation of the technique involving anesthetists from several centers in the UK and Ireland who routinely use mixtures. It has provided a snapshot of pediatric TIVA mixture use in the UK and Ireland, whilst demonstrating some of the differences in practice between centers.

There are a number of potential disadvantages to using propofol-remifentanil mixtures, including separation and layering, degradation of dilute remifentanil solutions, inability to alter individual target drug concentrations and lack of a license for the mixture[5,6]. However, a large proportion of drugs in pediatric practice are used off license[17]. Another potential disadvantage of mixtures is that both drugs are being delivered based on the PK properties of propofol. This leads to a gradual reduction in the propofol infusion rate over time for a given target concentration, as the propofol accumulates. Remifentanil does not accumulate, so the dose being delivered will gradually reduce. This is reflected in the median end-remifentanil infusion rate (0.09 $\mu g.kg^{-1}.min^{-1}$) being approximately half the median overall infusion rate (0.17 $\mu g.kg^{-1}.min^{-1}$). This could theoretically lead to inadequate delivery of remifentanil over time. However, as the median procedure duration was 32 minutes, the effect of propofol accumulation on reducing the remifentanil dose being delivered was manageable in most cases.

There were 55 patients in whom the Paedfusor model was used, despite their weight being above the maximum of 61 kg. After further assessment of these cases, it was clear that most were procedures where the propofol-remifentanil mixture was being titrated to effect, such as bowel endoscopy. In these circumstances, the absolute weight entered becomes less important, as the target concentration can be adjusted according to clinical signs. However, it was puzzling that the anesthetists did not choose to use an

adult model for these patients. Similarly, several small infants less than 5 kg in weight were managed with TCI, presumably by adjusting the propofol target concentration proportionate to the weight difference.

The most commonly used combination of propofol and remifentanil is 5 $\mu g.ml^{-1}$ remifentanil mixed with 1% propofol, or the equivalent with 2% propofol (PR5). The lower concentration of remifentanil allows most patients to maintain spontaneous ventilation and in certain cases maintenance of the airway without instrumentation. Overall complications and adverse events were significantly less common with PR5 mixtures, than with the higher remifentanil concentrations. Despite making up nearly 80% of the patients studied, the PR5 group suffered just over half the total complications seen.

The APRICOT study demonstrated an incidence of serious perioperative events of 5.2% of procedures[12], which is much higher than our evaluation at 1.7%. However, a secondary analysis of the APRICOT data from the UK demonstrated a lower overall incidence of 3.3%[18]. Our evaluation differed from APRICOT, as patient numbers were much smaller and it did not cover the full spectrum of pediatric anesthetic practice. However, the commonest severe critical event reported in APRICOT was laryngospasm, which occurs in all aspects of pediatric anesthesia. Although the serious complication rate is half that of APRICOT UK and even less than other earlier studies, the types of adverse events are different and mainly related to predictable effects of the drugs used. Apnea, bradycardia and chest/abdominal rigidity are all characteristic of administration of a potent opioid, such as remifentanil. Other adverse events such as desaturation and hypotension can also be related to opioid use. None of the serious complications were deemed to be life threatening and none caused significant short-term morbidity. All could be managed easily, when treatment was deemed to be necessary. Unexpected apnoea and desaturation were the commonest serious adverse events and in all cases responded to appropriate respiratory interventions. Bradycardia and hypotension were also relatively common serious complications, although the former did not need treating in over 80% of cases, reflecting the fact it was generally related to the use of a propofol-remifentanil combination, rather than an extreme physiological response to an insult, such as hypoxia or shock.

Laryngospasm occurred during gaseous induction in two patients, but there were no intraoperative of postoperative cases recorded. Given that the incidence of laryngospasm is quoted at 0.7-4% in previous studies[8-12,19,20], including APRICOT, we would have expected to see 6-35 cases in our series. The lack of such cases suggests that the propofol-remifentanil combination provides a protective effect. There were also very few other significant perioperative respiratory complications recorded compared with previous studies looking at this in children. Complications such as bronchospasm were not recorded. Cough

occurred mainly on induction and was probably related to the effect of a bolus dose of remifentanil, as all but two had an IV induction. This is commonly seen with potent opioids, where the drug is administered quickly[21-23].

The reporting of a possible case of awareness was worrying. Unfortunately we were not able to find out any further details of this case from the anesthetist involved. Examining the anesthetic data, the patient was 8 years old and underwent squint surgery with the PR5 mixture. No NMBD was administered for intubation and the propofol target concentration varied from 5 $\mu g.ml^{-1}$ down to a minimum of 4 $\mu g.ml^{-1}$. Movement was not recorded as an intraoperative complication and the patient did not wake up quickly at the end of surgery, taking 31 minutes to open their eyes. With the information available, it seems highly improbable that awareness occurred.

A limitation of our service evaluation is that it was reliant on individual reporting of cases and complications. We could not guarantee that all cases undertaken during the evaluation period were reported, which could have lead to some bias. Most of the anesthetists participating in this evaluation were regular TIVA users in children, which may also have had some influence on the complication rate. It is feasible that in less experienced hands the complication rate will be higher. However, this is likely to be minimized if ≤PR5 is used as the mixture.

The reasons why ≤PR5 patients had a lower incidence of complications is possibly due to the lower initial bolus dose of remifentanil and the lower infusion rate during surgery. Many of the serious complications seen such as apnoea, bradycardia, hypotension and rigid abdomen/chest, were primarily related to the use of remifentanil and likely dose-related. It is also possible that the type of procedure being undertaken influenced the occurrence of complications. A high proportion of the ≤PR5 patients were undergoing a bowel endoscopy procedure without airway instrumentation, where lighter anaesthesia with maintenance of spontaneous ventilation is essential for the technique to be successful.

Recent AAGBI guidance has stated that the use of mixtures of propofol and remifentanil is not recommended, albeit with little evidence to back this statement up[24]. Whilst we accept that the use of mixtures is controversial, this has become standard practice in a number of pediatric centers in the UK and Ireland. Our service evaluation shows that when administered to pediatric patients by experienced TIVA users, there is a very low incidence of serious, related, unexpected adverse events. When these occur, they are largely related to the pharmacodynamics of the drugs being used and readily amenable to simple interventions. Life-threatening adverse events were not experienced by any patient. We recommend that anyone wishing to gain experience of this technique in children should start with the ≤PR5 mixture, as this

appears to have a lower incidence of complications than combinations with a higher concentration of remifentanil.

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Table 1. Demographic data.

Age (years)	n	Weight (kg)	n
<1	38	**<10**	62
1-5	333	**10-19.9**	274
6-10	266	**20-39.9**	322
11-16	175	**40-69.9**	189
>16	39	**>70**	23
No data	22	**No data**	3

Table 2. Surgical specialties represented and incidence of complications in relation to remifentanil concentration administered.

Specialty	Number of patients (%)	Remifentanil groups – percentage incidence of any complication		
		≤5 μg.ml^{-1}	≥10 μg.ml^{-1}	Overall complications (%)
Gastroenterology	181 (20.7%)	10.6%	27.3%	11.6%
ENT Surgery†	180 (20.6%)	10.5%	48.1%	16.1%
Dental/Maxillofacial Surgery	131 (15.1%)	10.2%	30.3%	15.3%
General Surgery	126 (14.4%)	17.2%	38.7%	27.8%
Plastic Surgery	87 (10%)	10.6%	50%	11.5%
Orthopaedic Surgery	45 (5.2%)	23.1%	33.3%	24.4%
Neurology/Neurosurgery	30 (3.4%)	3.6%	0%	3.3%
Urology	26 (3%)	53.8%	61.5%	57.7%

Ophthalmology	20 (2.4%)	40%	100%	42.9%
Radiology/Imaging	8 (1.1%)	12.5%	50%	20%
Others‡	23 (4.1%)	8.7%	38.5%	19.4%

†ENT – Ear, Nose and Throat

‡Rheumatology, Hepatology, Medicine, Cardiology, Haematology/Oncology, Undefined (all 1% or less)

Table 3. Propofol target concentrations during the procedures.

Propofol target concentration ($\mu g.ml^{-1}$)	Median	Range	IQR
Initial	4	1-7	1
Maximum	4	1.5-8	0.7
Minimum	2.9	0.7-6.5	1.5
End	2.9	0.7-6	0.6

IQR; interquartile range

Figure 1. Values for end-remifentanil rates in $\mu g.kg^{-1}.min^{-1}$ for different remifentanil concentrations calculated from the final propofol infusion rate. There was no data for PR2.5 mixtures.

Remifentanil concentration in $\mu g.ml^{-1}$; Remifentanil rates in $\mu g.kg^{-1}.min^{-1}$

Table 4. Numbers of all listed complications occurring during induction, maintenance and recovery of anaesthesia. Figures in brackets indicate the number that required interventions.

Complication	Induction	Maintenance	Recovery	Total
Desaturation	25 (21)	4 (2)	14 (10)	43 (33)
Cough	29 (13)	4 (4)	7 (3)	40 (20)
Apnoea	8 (8)	12 (12)	12 (12)†	32 (32)

Movement	4 (4)	25 (23)	n/a	29 (27)
Pain	6 (2)	n/a	7 (4)	13 (6)
Bradycardia	4 (0)	6 (2)	1 (0)	11 (2)
Hypotension	0	8 (7)	1 (0)	9 (7)
Abdominal/chest rigidity	7 (5)	2 (2)	0	9 (7)
LMA problems	3 (2)	2 (2)	n/a	5 (4)
Agitation	1 (0)	n/a	4 (0)	5 (0)
Hypoventilation	1 (0)	4 (0)	0	5 (0)
Others	12 (10)‡	3 (3) §	8 (2)¶	23 (15)
Total	100 (65)	70 (57)	54 (31)	224 (153)

†11 patients brought into recovery apnoeic from theatre

‡Included airway obstruction (3), chest problems (3), laryngospasm (2), cannula displacement (1), fighting ventilator (1), pump failure (1), derecruitment (1)

§Included IV line occlusion (1), irregular respiratory pattern (1), bleeding (1)

¶Included delayed recovery (2), postoperative nausea & vomiting (2), low oxygen saturations above 90% (1), secretions (1), stridor (1), possible awareness (1)

Table 5. Serious, unexpected, related complications requiring intervention. There were none recorded in the postoperative period.

Patient	Age (years)	Weight (kg)	ASA	Speciality	Procedure	Mixture	Induction complication	Intervention	Intraoperative complication	Intervention
1	1.82	15	1	General Surgery	EUA & laparoscopy	PR10	Cough	Paralysed	-	-
2	2.86	8.8	3	General Surgery	Hickman line insertion	PR10	Cough	Paralysed	-	-
3	3.24	12.7	3	Radiology	Angiography	PR10	-	-	Hypotension	Fluid bolus
4	3.84	16	1	Haematology/Oncology	Bone marrow harvest	PR10	Rigid chest	Increased ventilator pressure	-	-
5	3.97	26	1	Plastics	Suturing laceration	PR5	Apnea/Desaturation (<90%)	Hand ventilation	-	-
6	5.04	21	2	Ophthalmology	Squint correction	PR5	Apnea/Desaturation (<90%)	Hand ventilation	-	-
7	5.19	20	1	General Surgery	Umbilical hernia repair	PR10	Desaturation (<90%)	Hand ventilation	-	-
8	5.85	22	2	Ear Nose & Throat	Grommets & adenotonsillectomy	PR5	Cough	Local anesthetic to vocal cords	Apnea	IPPV/PS

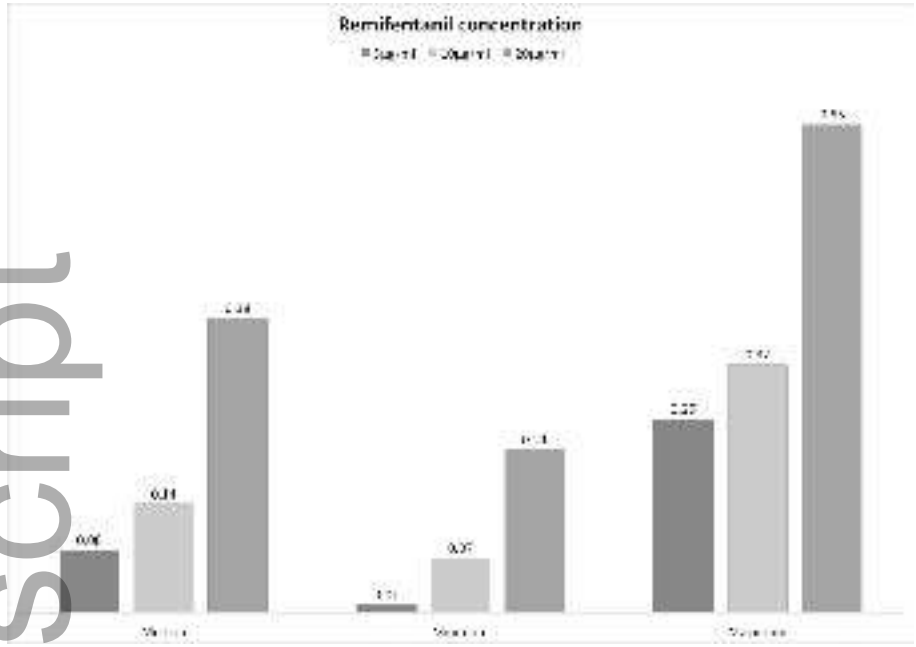
9	5.89	17.9	3	Urology	Liver biopsy, cystoscopy & stent exchange	PR10	Apnea/Desaturation (<90%)	Hand ventilation	-	-
10	7.45	20	1	Urology	Hypospadias repair	PR10	Rigid Chest Desaturation (<90%)	Hand ventilation	-	-
11	7.63	27	3	General Surgery	Hickman line insertion	PR10	Breathing against ventilator	Paralysed	-	-
12	10.10	29	2	Gastroenterology	OGD and Biopsy	PR5	-	-	Apnea	Jaw thrust
13	13.64	47	3	General Surgery	Hickman line insertion	PR10	-	-	Irregular breathing	Paralysed & IPPV
14	14.70	66	2	Gastroenterology	OGD	PR5	-	-	Apnoea	Jaw thrust
15	15.49	56	1	Gastroenterology	OGD	PR5	Apnea/Desaturation (<90%)	Hand ventilation & reduced propofol	-	-

OGD – Esophagoscopy, gastroscopy, duodenoscopy; IPPV – Intermittent positive-pressure ventilation; PS – Pressure support;

Table 6. Relationship between the remifentanil concentration and the incidence of complications.

Remifentanil concentration	Number of patients (%)	Number of patients with complications	Percentage of all patients with complications
2.5	13 (1.5%)	1	0.6%
5	688 (78.8%)	92	57.9%
10	121 (13.9%)	49	30.8%
20	51 (5.8%)	17	10.7%

Total	873 (100%)	159	100%



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