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Propofol doses differ in total intravenous anaesthesia (TIVA) for cancer and no cancer surgery – observational cohort study

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Abstract. – OBJECTIVE: Propofol (2,6-diisopropylphenol) is a broadly used anaesthetic in total intravenous anaesthesia (TIVA) that might alter course of disease in patients who underwent oncology surgery. High inter-individual variability of the propofol dose needed for the same level of consciousness during surgical tumour removal is influenced by many factors.

PATIENTS AND METHODS: This is a retrospective observational cohort study of prospectively collected patients data over 20 month's period. The main endpoint of the study was to compare propofol consumption needed for cancer and no cancer surgical interventions. The secondary endpoints were to find out whether there is a difference in recovery time between the two groups of patients and to reveal potential correlations between propofol consumption and age, duration of anaesthesia, body weight and Charlson co-morbidity index (CCI) in cancer and no cancer surgery.

RESULTS: There were 103 patients with cancer (mean age 59.3 yr ± 10.7) and 109 patients operated due to other reasons (mean age 47.6 yr ± 17.52). Female sex predominated in both groups (70.9% in cancer and 67.9% in no cancer patients). They differed regarding CCI, 4.48 (±2.1) in cancer in contrast to 1.49 (±1.83) in no cancer patients, and anaesthesia time, 92.67 minutes ± 46.15 *vs.* 75.24 ± 37.28, respectively ($p = 0.0012$). Propofol induction dose did not differ significantly between the two groups ($p = 0.193$), while total propofol consumption was 85.86 mcg/kgBW/min (± 25.98) in cancer and 95.77 (± 31.48) in no cancer patients ($p = 0.01$). Propofol consumption negatively correlated with duration of anaesthesia and body weight in cancer group. However, in no cancer patients there was very strong negative association with age, duration of anaesthesia and CCI, and significant but weaker negative association with body weight. The time to awakening did not differ significantly between the groups ($p = 0.219$).

CONCLUSIONS: Propofol dose differed in cancer comparing to no cancer patients under general anaesthesia. There was no need for dose adjustment regarding the age and sex in patients with cancer in contrast to no cancer surgery.

Key Words:
Propofol, Dose, Anaesthesia, General, Cancer.

Introduction

Propofol (2,6-diisopropylphenol) has been broadly used anaesthetic for more than three decades, since its introduction in Europe in 1986[1]. Different factors influence variable sensitivity to propofol and have impact on the precise and individualised dose evaluation[2]. New data reveal that propofol might have a role in the postoperative course in the patients with cancer. Its impact on the outcome of the disease depended on the affected organs and the specific characteristics of tumour cells[3, 4]. In a large retrospective cohort study, Wigmore et al[5] evaluated long-term survival in patients receiving inhalational comparing to group with total intravenous anaesthesia (TIVA) using remifentanil and propofol. Their results show that, especially for patients undergoing gastrointestinal surgery, outcome was better in TIVA group regardless of the American Society of Anesthesiologists physical status (ASA) score, surgical intervention performed, or presence of metastasis. Additionally, Shaefer et al[6] reported that propofol reduced 1-year mortality in patients with non solid tumour surgery in a dose dependent manner. Beneficial effects of propofol were reported for breast cancer surgery as well[7]. However, other retrospective studies reported no influence on the course of the disease after cancer operations under propofol or inhalation anaesthesia, independently of which organ was affected[8-10]. Furthermore, Enlund et al[11] also retrospectively examined patients' survival after breast, colon and rectal cancer surgery. Their findings were inconclusive regarding anaesthetics used.

Some studies elucidate the mechanisms of how propofol promotes tumour growth and metastatic capacity in gallbladder and breast cancer[12,13]. Others, in contrast, highlight inhibitory effect of

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propofol on malignant cells invasion, migration, growth and self-renewal[3,14]. Thus, according to the published data, propofol can activate apoptosis and consequently block cancer cell proliferation or inhibit glycolysis in colorectal cancer cells[3,15]. Molecular mechanism of propofol`s anti-cancer activity is not clear. Action through microRNAs and reduction of matrix metalloproteinase expression with consequent changes of anti-cancer microenvironment deserves attention[16]. Animal studies suggest that thanks to its anti-inflammatory effects, propofol decreases mortality rate by endotoxin shock in rats[17]. In line with this, Ke et al[18] reported lower level of tumour necrosis factor alpha (TNF-alpha) and interleukine-6 (IL-6) as a response to stress of surgery with TIVA using propofol at the end of operation. They also found higher interleukine-10 (IL-10) level 12 hours after the operation. However, in a meta-analysis facing inflammatory response as a function of anaesthetic technique, O'Bryan et al[19] recently stated that, in spite of high heterogeneity in the studies, there was no difference between TIVA using propofol and inhalational anaesthesia. There is still debate regarding precise determination of propofol dosage, bearing in mind lots of potentially relevant factors. In regard with the patients' sex, majority of studies reported that women needed more propofol for the same level of consciousness and that they emerged faster than men from propofol anaesthesia[20-25]. However, Choi et al[26] found that male patients require a higher dose of propofol than female for I-gel insertion. Factors that contribute to propofol consumption for induction and maintenance of general anaesthesia are also the level of anxiety[27], obesity[28,29], and the way of monitoring the depth of anaesthesia[30]. Pharmacogenetic discoveries are not yet broadly implemented in anaesthesia as a routine practice. However, there are a lot of scientific information that help tailor more precise medication according to genetic profile of an individual patient. In order to minimize adverse drug reactions, Zarei et al[31] collected drug-gene interactions with focus on perioperative setting. Due to low pharmacogenetic knowledge in anaesthesiology, they constructed a web-based application with possibility to predict drug reactions connected with more than one genetic variation. Jhun et al[32] reviewed the role of pharmacogenetics in perioperative practice. They analyzed the most frequently used drugs in this setting and genetic polymorphisms that might influence their pharmacodynamic effects. This review involved neuromuscular blocking drugs (succinylcholine and mivacurium), volatile anaesthetics (desflurane, isoflurane, sevoflurane), analgesics (morphine, codeine, tramadol) and propofol. It is identified that ethnicity participates in the determination of the propofol dose needed, as well[33-35]. In line with these facts is the exploration of the role of genetics as a cause for inter-individual variability of propofol dose needed for induction and maintenance of anaesthesia. Therefore, Zakerska-Banaszak et al[36] conducted a study to identify genetic base of individual response to propofol on the Polish patients` group. Similarly, in the same ethnic group, Mikstacki et al[37] explored genetic polymorphism responsible for metabolism of propofol and its anaesthetic activity. Likewise, Mourão et al[38] found that the presence of T allele of cytochrome p450 was responsible for the need of lower dose of propofol. To our knowledge, no data on the differences between propofol induction and maintenance dose in cancer and no cancer surgery performed in total intravenous anaesthesia have been published so far. Concerning a large share of oncological surgery, the main endpoint of our study was to compare propofol consumption needed for cancer and no cancer operations. The secondary endpoints were to find out whether there is a difference in recovery time between the two groups of patients and are there correlations with total propofol consumption and age, duration of anaesthesia, body weight and Charlson co-morbidity index in cancer and non cancer surgery patients.

Patients and Methods

Design and Setting

This is retrospective observational cohort study of prospectively collected patient data from Clinical Centre of Montenegro (Podgorica) over two years (from February 2018 to October 2019). The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee of the Faculty of Medicine in Podgorica (Montenegro) approved the study (No 433/3) on 16.03.2022.

Patient Enrolment

All adult patients scheduled for elective surgery under total intravenous anaesthesia using propofol were consecutively recruited. Criteria for exclusion were emergent surgery, concomitant chemotherapy, anticipated bleeding during surgery, massive intra-operative blood transfusion, drug and alcohol addiction, age less than 18 years, use of inhalation anaesthetics, addition of regional anaesthesia, any contraindications for using propofol and missing data during transcription.

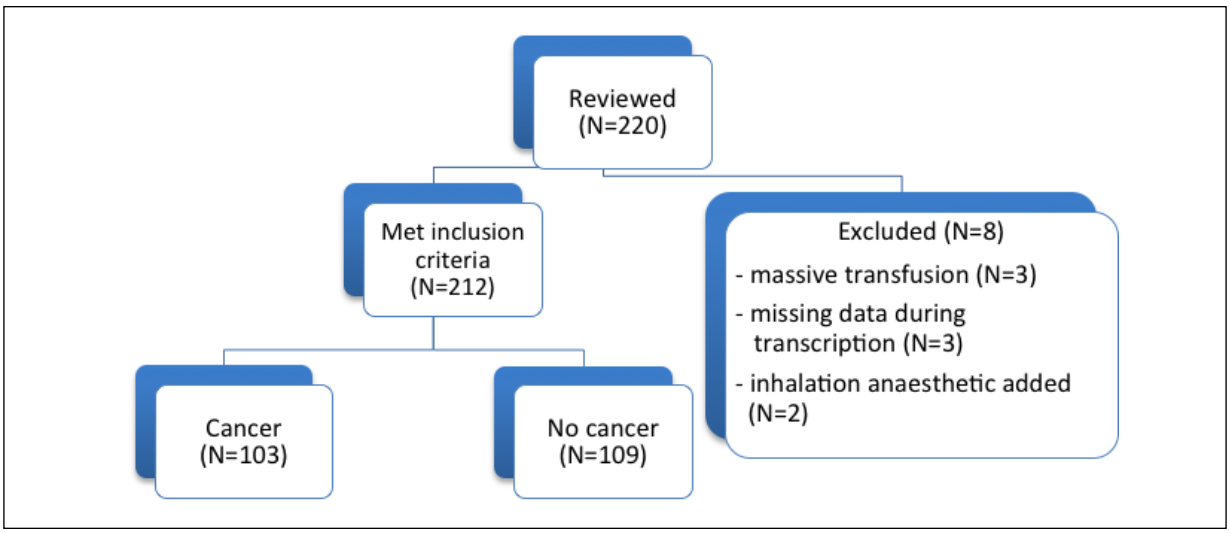

Figure 1. Flow diagram of patients' selection.

All patients were scheduled for routine surgical program, and they signed informed consent as a rule. No specific randomisation was performed regarding research, as all data analyzed have been monitored as usual everyday practice. All anaesthesia procedures included were performed by the same team. For this study, data were rewritten from anaesthesia sheet to the research protocol form focusing on the primary and secondary endpoints (**Supplementary Table I**).

Selection of patients included is shown on the flow diagram (Figure 1).

Anaesthesia Technique

Patients' heart rate (HR) using 3- or 5-lead electrocardiography, non-invasive systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP) at a 5 min intervals and peripheral oxygen saturation (SpO_2) with Drager Infinity Kappa monitor were recorded after arrival in the operating theatre and during anaesthesia until the full awakening. At the same time, bispectral index (BIS) sensor was placed on each patient frontally (Covidien BIS Quatro Sensor XP Platform X) and connected to a BIS Vista monitor (Covidien, Aspect Medical system). Then, BIS value was noted (with a smoothing rate of 10 seconds. These data were recorded as the basal values (time 0 or T0). After establishing intravenous line, preoperative medication was applied 30-45 min before induction in anaesthesia. The dose and drugs were determined in compliance with the suggestion of anaesthesiologist in charge during pre-anesthesia visit evaluation (atropine sulphate 0.5 mg and midazolam 70-80 mcg/kg intramuscularly) and adapted accordingly to the assessed level of anxiety. Slow infusion of Ringer's lactate solution (5-10 ml/kg) was installed and non invasive blood pressure, HR, SpO_2 and BIS values were recorded 30 min after premedication (T1). Induction in anaesthesia started with bolus dose of fentanyl 100 µg intravenously followed by manually controlled propofol infusion (1%, Diprivan, Astra Zeneca) applied by the infusion pump (B Braun Infusomat Space Infusionpump). The same pump was used for the maintenance of anaesthesia with the speed of 200-400 ml/h (depending on the patients' weight, ASA status and hemodynamic parameters), until a drop of BIS values (in the range of 70-60) and a loss of consciousness. Unconscious state was assessed by no response to mild touch and a loss of eyelash reflex. This technique was used in order to apply the smallest effective dose and to avoid unwanted effects. Subsequently, the rate of infusion was set according to the stabilisation of BIS values (in a range 40-60). Intubation dose of rocuronium bromide (0.6 mg/kg) was administered intravenously and tracheal intubation was performed 3 minutes later. The dose of propofol needed for tracheal intubation without marked changes in blood pressure and heart rate (±30% of basal) and BIS ≤60 was considered as induction dose. All monitored parameters were then recorded as T2. Patients were artificially ventilated (FiO_2=0.33, Air=0.66, tidal volume 6-8 ml/kg, 10-12 breaths/min, depending on $ETCO_2$) on anaesthesia machine Primus (Drager). Parameters measured at the time of surgical incision were recorded as time 3 (T3). The depth of anaesthesia was maintained in

the BIS range of 40-60 by manually regulating the speed of propofol infusion, delivered by the same infusion pump. Fentanyl was added repeatedly in a bolus dose of 50-100 mcg intravenously and rocuronium in a bolus dose of 0.1-0.2 mg/kg. Twenty minutes after induction of anaesthesia parameters were recorded again (time 4=T4). Due to renal problems, only 5 patients received cysatracurium instead of rocuronium, and one patient received remifentanyl in continuous infusion instead of fentanyl. Infusion rate of propofol was decreased at the beginning of the surgical wound closure and its administration stopped simultaneously with the last suture. Parameters measured at this time were recorded as T5 (end of surgery). At that time, reversal of muscle relaxant was given (neostigmine 2.5 mg and atropine sulphate 1 mg, in the same syringe, as a slow intravenous bolus). Due to prolonged muscle relaxation, 3 patients received shugamadex for rocuronium wash out. Total amount of intravenous fluids given to all patients was recorded, too. All monitored parameters were evidenced after the tracheal tube removal, which corresponded to time 6 (T6). Recovery time was measured and recorded for each patient, counting from the point when propofol was discontinued to the spontaneous eye opening, normal breathing pattern, successful accomplishment of simple verbal commands, and BIS values at least 75.

Data Collection

Demographic and clinical data collected for each patient were: age, weight, ASA status, co-morbidities, Charlson co-morbidity index (CCI), surgical diagnosis, type and duration of surgery and medication for chronic diseases (Table I).

Table I. Patients' characteristics and baseline parameters.

Variable	Cancer (n=103) (%)	Cancer median (25%/75% percentile)	No cancer (n=109) (%)	No cancer median (25%/75% percentile)	*p*-value
Gender † (male/female)	30/73 (29.1/70.9)		35/74 (32.1/67.9)		*p*=0.6576 (95% CI, 0.4814 -1.548) OR 0.8689
Age (years), mean (± SD)	59.3 (±10.7)	60.5 (52/67)	47.6 (±17.52)	48.00 (32/63.5)	***p*<0.0001******
Age † 18-55 yr (%) >55 yr (%)	 33 (32.3%) 69 (67.7%)		 63 (57.8%) 46 (42.2%)		***p*=0.0003***** (95% CI, 0.2007-0.6116) OR 0.3492
B W (kg), mean (± SD)	77.4 (±13.9)	75.0 (70/85)	76.8 (±13.4)	78.0 (65.5/86.5)	*p*=0.999
ASA I/II (%)	33 (32)		69 (63)		
ASA III/IV (%)	70 (68)		40 (37)		
CCI mean (± SD)	4.48 (±2.1)	4.0 (3.0/5.25)	1.49 (±1.83)	1.0 (0.0/2.0)	***p*<0.0001******
BIS 0 mean (± SD)	94.9 (±3.14)	96.0 (94/97)	95.4 (±3.31)	97 (94/98)	*p*=0.163
SBP 0 (mmHg), mean (± SD)	142.7 (±27.71)	140.0 (128.0/157.0)	137.9 (±19.72)	135 (125.0/147.0)	*p*=0.062
DBP 0 (mmHg), mean (± SD)	82 (±11.7)	83.0 (73/90)	80.3 (±10.9)	80.0 (73.5/87)	*p*=0.1325
MAP 0 (mmHg), mean (± SD)	102 (±13.6)	103 (93/110)	99 (±12.15)	98 (91/107.5)	*p*=0.0804
HR (min) mean (±SD)	76.6 (±14.15)	75 (68/82)	79.7 (±14.9)	78 (45/87.7)	*p*=0.0961
Arterial hypertension N (%)†	46 (44.7%)		39 (35.8%)		*p*=0.2085 (95% CI 0.835-2.544), OR 1.448
Obesity, N (%) †	15 (14.6%)		15 (13.8%)		*p*>0.999 (95% CI 0.4908-2.313), OR=1.068
Diabetes, N (%) †	10 (9.7%)		13 (11.9%)		*p*=0.6628 (95% CI 0.3313-1.948), OR 0.7940

† Fisher's exact test. SD – standard deviation. Continuous variables are presented as mean ± SD, whereas discrete variables are presented as number (proportion). BW – body weight, ASA – American Society of anaesthesiologists physical status, CCI – Charlson co-morbidity index, BIS 0 – bispectral index value at time 0, SBP 0 – systolic blood pressure at time 0, DBP 0 – diastolic blood pressure at time 0, MAP 0 – mean arterial blood pressure at time 0, HR 0 – heart rate at time 0 (beats per minute). *** $p < 0.001$, **** $p < 0.0001$.

Parameters routinely monitored during TIVA anaesthesia were transcribed on the study sheet: heart rate (HR), non-invasive systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO_2) and BIS values. Following time points were chosen as reliable for the endpoints of the study:

T0=basal values (at the arrival to the operating theatre)

T1=values after preoperative medication

T2=values at the induction of anaesthesia (tracheal intubation)

T3=surgical incision

T4=20 minutes of induction

T5=end of surgery

T6=after extubation

Propofol induction dose as well as its total consumption, total amount of intravenous fluid, fentanyl (or remifentanyl), rocuronium bromide (or cysatracurium), rescue medication during or at the end of surgery were recorded for each patient and for every given time point.

Statistical Analysis

Obtained data were statistically analysed using GraphPad Prism 9.3.1. (GraphPad Software Inc, San Diego, CA, USA). All continuous variables were first tested for normality of distribution by D`Agostino-Pearson and Shapiro-Wilk tests. For normally distributed continuous data descriptive statistics were presented as mean ± standard deviation and for categorical data as numbers and percentages. Non-normally distributed continuous data were presented as median (25%-, 75%-percentile). Discrete variables are presented as a number (95%-confidence intervals). Continuous variables were analyzed with t-test or one-way ANOVA (normally distributed), or with non-parametric tests such as Kolmogorov-Smirnov or Mann-Whitney test (not normally distributed). The results were considered statistically significant when $p<0.05$. Strength of correlation between continuous variables was assessed by Pearson's correlation, whereas Fisher`s exact test was used for correlation between categorical variables. Multiple linear regressions were used to find a model that predicts total propofol levels from the other variables analysed.

Results

Patients' characteristics and baseline parameters are shown in the Table I. All patients were Caucasians, Montenegrin ethnicity. Female gender dominated in both groups. As it was expected, there was significant difference between cancer and no cancer group of patients concerning the age, Charlson co-morbidity index (CCI) and ASA status. Basal values of BIS, mean arterial pressure, systolic and diastolic blood pressure and pulse rate did not differ significantly. The most frequent co-morbidities were obesity, arterial hypertension and diabetes, but their contribution did not significantly differ between the two groups. Eight different kinds of surgery in cancer group and 10 in no cancer were performed and they differed significantly in anaesthesia time (Table II). Duration of anaesthesia was significantly longer in cancer operations, but neither the time to awakening nor fentanyl dose was significantly different between the groups. The consumption of the most frequently used neuromuscular blocker, rocuronium, was significantly higher in no cancer surgery group. BIS value at the end of surgery (T5) was significantly higher in no cancer patients, but the difference was not significant after tracheal tube removal (T6).

Table II. Variables related to anaesthesia: anaesthesia time, induction dose and total consumption of propofol, fentanyl, rocuronium and awakening time. * $p < 0.02$, ** $p < 0.002$.

	Cancer (n=103) mean (± SD)	Cancer median (25%/75% percentile)	No cancer (n=109) mean (± SD)	No cancer median (25%/75% percentile)	*p*-value
Duration of anaesthesia (min)	**92.67 (±46.15)**	**80 (60/120)**	**75.24 (±37.28)**	**65.00 (55/80)**	***p*=0.0012 ****
Propofol induction dose (mg/kgBW)	1.178 (±0.382)	1.100 (0.900/1.375)	1.235 (±0.404)	1.200 (0.945-1.500)	*p*=0.1935
Propofol total consumption (mcg/kgBW/min)	**85.86 (±25.98)**	**83.33 (68.15-99.16)**	**95.77 (±31.48)**	**94.44 (73.18-116.3)**	***p*=0.0103 ***
BIS 5	**56.7 (±9.9)**	**58 (50/63)**	**60.6 (±11.02)**	**60 (53/68)**	***p*=0.0129 ***
BIS 6	83.8 (±5.98)	83 (80/88)	84.7 (±6.4)	85 (80/90)	*p*=0.169
Fentanyl dose (mcg/kgBW)	3.7 (±0.96)	3.53 (3.08/4.17)	3.43 (±0.87)	3.33 (2.86/3.85)	*p*=0.0646
Rocuronium dose (mg/kgBW)	**1.03 (±0.44)**	**1.00 (0.80/1.23)**	**0.92 (±0.418)**	**0.88 (0.71/1.06)**	***p*=0.0108 ***
Awakening time (sec)	300.7 (±145.6)	300.0 (210/360)	282.0 (±141.7)	270.0 (220/330)	*p*=0.2194

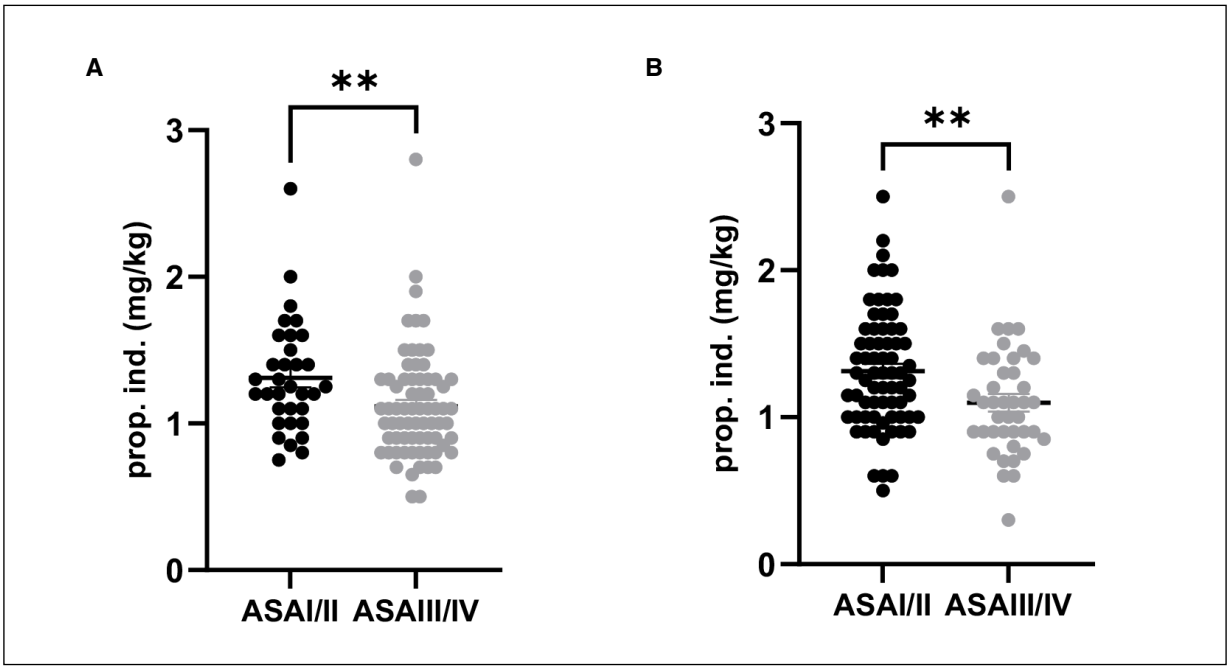

Figure 2. Propofol induction dose *vs.* ASA physical status.

Propofol induction dose (mg/kgBW) did not differ significantly between the two groups, but there was a significant difference between the groups depending on ASA status (Figure 2).

Analysis of the relationship between propofol induction dose and age showed that in cancer patients there was not statistically significant difference between younger (18-55 yr) and older subgroup (>55yr) (Table III). On the other side, in the no cancer group, induction dose was significantly higher in the younger patients group**.** Although induction dose did not differ between the groups, if subdivided and compared according to the type of surgery, significant difference was found for gynaecological operations. In cancer group mean propofol dose (mg/kgBW) was 1.208 (SD ±0.3232, median 1.3, 95% CI 0.837-1.50), and in no cancer it was 1.45 (SD± 0.417, median 1.40, 95%CI 1.10-1.65), p=0.047* (**Supplementary Table II**).

Since total propofol consumption (mcg/kgBW/min) was significantly higher in no cancer group of patients (p=0.01), we next stratified patients according to the type of surgery. Statistically significant difference was found only for ENT surgery, where higher total propofol consumption was found in no cancer compared to cancer group (Table IV).

Considering the relationship between propofol consumption and age, there was no significant difference in the two groups of cancer patients (18-55 yr *vs.* > 55 yr), but in no cancer group, younger patients needed significantly higher propofol dose during operation (Table V). We further analyzed

Table III. Propofol induction dose *vs.* age. ** $p < 0.01$.

AGE, yr (n)	propofol (mg/kgBW), median (25%/75% percentile)	propofol (mg/kgBW). mean (± SD)	*p*-value (Mann-Whitney)
Cancer, age 18-55 yr (n=33)	1.250 (0.9500/1.500)	1.247 (±0.3588)	0.0933
Cancer, age >55yr (n=71)	1.100 (0.900/1.300)	1.146 (±0.3909)	
No cancer, age 18-55 (n=64)	1.300 (1.000/1.600)	1.313 (±0.4050)	**0.0088 ****
No cancer, age >55yr (n=45)	1.100 (0.900/1.400)	1.124 (±0.3847)	

Table IV. Total propofol consumption in cancer and no cancer patients regarding the type of surgery. †ENT – ear, nose and throat. ** $p < 0.01$.

Type of surgery (no of cancer/ no cancer patients)	Cancer Tot propofol (mcg/kgBW/min) median (25%/75% percentile)	Cancer Tot propofol (mcg/kgBW/min), mean (±SD)	No cancer Tot propofol (mcg/kgBW/min), median (25%/75% percentile)	No cancer Tot propofol (mcg/kgBW/min) mean (±SD)	*p*-value
Breast (26/3)	82.1 (72.50/103.1)	88.33 (29.22)	112.1 (97.92/114.3)	108.1 (8.89)	0.067
Lung surgery (22/6)	83.57 (67.56/103.2)	83.90 (23.54)	102.1 (81.31/118.1)	97.00 (27.37)	0.235
Thyroid surgery (18/17)	86.65 (49.79/96.81)	78.81 (25.58)	92.59 (75.75/108.9)	95.26 (22.32)	0.590
Gynaecology (18/22)	88.68 (71.05/106.5)	94.71 (30.23)	97.78 (85.21/129.6)	109.6 (34.3)	0.142
ENT† (7/26)	91.52 (74.07/106.2)	88.22 (15.87)	116.7 (97.30/134.5)	115.1 (26.14)	**0.007** **
Urology (6/4)	70.59 (60.42/85.03)	73.09 (14.15)	64.93 (62.89/77.67)	68.50 (8.86)	0.9619
Digestive surgery (5/12)	74.32 (64.44/95.83)	78.98 (17.19)	72.59 (58.90/81.96)	71.82 (14.74)	0.442

younger and older female sex as predominant. Result showed significantly different propofol consumption in no cancer group (higher doses were needed for younger women), while in cancer females there was no significant difference between the two age categories (Table VI). As it was the case with the induction dose, total propofol consumption was significantly higher in ASA I/II *vs.* ASA III/ IV group in both, cancer and no cancer patients.

Next, we sought to explore the potential impact of the most frequent co-morbidities on propofol dose in both groups of patients (Table I). Hypertension predominated, contributing with 44.66% in cancer and 35.78% in no cancer patients (95% CI, 0.835-2.544, OR 1.448 p=0.208). Comparing these subgroups according to the propofol needed, no significant difference between cancer and no cancer patients was found (mean propofol consumption rate for cancer was 80.21 mcg/kg/min, SD ±21.35, St error 3.148, and for no cancer it was 82.0 mcg/kg/min, SD 22.73, St error 3.64, 95% CI: -7.730 to 11.31, p=0.709). Obesity participated as a second most frequent co-morbidity of potential importance for propofol dosage. There were 14.56% patients with obesity diagnosed before surgery in cancer and 13.76% in no cancer group. Mean propofol consumption in cancer obese patients was 75.71 mcg/kg/min, SD ±16.56, St error 4.277, and in no cancer subgroup 86.56 mcg/kg/min, SD ±22.85, St error 5.899 (95%CI -4.076 to 25.77, p=0.1477). In order to identify whether age, duration of anaesthesia, body weight and Charlson co-morbidity index (CCI) influence total propofol consumption in cancer and no cancer patients, we tested for these variables. There was weak negative correlation with duration of anaesthesia and body weight in cancer group but no significant correlation was found with age and CCI (Table VII). In no cancer group correlation analysis showed very strong negative association with age, duration of anaesthesia and CCI, and significant but weaker negative association with body weight (Table VIII).

In order to test the impact of following independent variables: age, body weight, sex, and the most influential co-morbidities (hypertension, diabetes, obesity and cardiovascular diseases) on propofol consumption, we conducted multiple linear regressions analyses. Significant association was not found in cancer group, but in no cancer there was negative association with age

Table V. Total propofol consumption depending on age in cancer and no cancer surgery patients.

Age, yr (n)	Tot propofol (mcg/kg/min) Median (25%/75% percentile)	Tot propofol (mcg/kg/min) Mean (± SD)	*p*-value (Mann-Whitney)
Cancer 18-55 yr (n=32)	87.70 (74.72/103.9)	91.74 (±32.78)	0.1959
Cancer >55 yr (n=70)	81.34 (66.09/96.02)	82.21 (±20.46)	
No cancer 18-55 yr (n=63)	103.2 (80.41/122.2)	104.9 (±31.22)	**0.0001*** **
No cancer >55yr (n=45)	81.63 (64.14/96.36)	83.05 (±27.83)	

*** $p < 0.0001$.

Table VI. Total propofol consumption in female patients for cancer and no cancer surgery depending on age. * $p < 0.05$.

Females (n)	Tot propofol (mcg/kg/min) Median (25%/75% percentile	Tot propofol (mcg/kg/min), mean (±SD)	*p*-value (Mann-Whitney)
CancerAge 18-55 yr (n=27)	87.63 (75/106.2)	95.17 (±32.75)	*p*=0.1095
Cancer Age >55 yr (n=45)	81.25 (64.77/98.76)	81.61 (±21.26)	
No cancer Age 18-55 yr (n=45)	102.0 (80.20/124.0)	107.5 (±32.56)	***p*=0.0342 ***
No cancer Age >55 yr (n=28)	85.11 (71.91/104.4)	91.40 (±27.93)	

(95%CI -1.021 to -0.1347, p=0.011) and male sex (95%CI -31.38 to -3.006, p=0.018), shown in Tables IX and X.

Discussion

It is estimated that by 2030, there will be about 45 million surgeries yearly due to oncological reasons worldwide[39]. Romito et al[40] report that about 80% of surgical interventions are performed with the use of propofol. In our study, there was significantly lower total consumption of propofol in patients undergoing cancer surgery, compared to no cancer patients. However, no statistical difference was found between the two groups in the induction dose of propofol. Moreover, in contrast to patients operated for no cancer reasons, in patients with cancer there was not statistically significant difference in propofol dose regarding age, for induction as well as total consumption. No significant association was found between propofol consumption and age, sex or CCI in cancer patients as opposed to not cancer group. These results suggest that, towards precision anaesthesia, no dose adjustments are needed for age, gender and CCI in cancer patients**.** A few decades ago, Kreuer et al[41] suggested a formula to calculate the need for propofol consumption and recovery time, describing a decreased need in older age. Still, they admitted high inter-individual variability that unable dose prediction only according to patients' age. Later on, Eleveld et al[42] stated that reduced infusion rate in older age is required, proposing pharmacokinetic model based on the relationship with weight, age and sex. Soon after, Chan et al[43] also reported inverse correlation with age and propofol dose in patients who underwent surgery under TIVA anaesthesia with propofol. Along with the age, sex is also reported as an important predictor of propofol dose, but with less consistent conclusions. Hence, Vuyk et al[44] studied pharmacokinetic model of propofol delivered by continuous infusion in patients of both sexes, older than 65 years. They found that elderly females needed about 10% higher infusion rates to reach the same blood concentration as males. Additionally, a decrease in propofol dosage of 0.46 mg $kg^{-1}h^{-1}$ per decade of life in women and 0.28 mg kg^{-1} h^{-1} in men was proposed[22]. Studies also revealed higher level of early propofol metabolites in women between 35 and 64 years of age[23,24]. These data are in line with our results regarding propofol dose in the group of patients undergoing no cancer surgery (strong negative association with age). Maeda et al[20] analyzed propofol infusion rate and four parameters: age, body weight, midazolam co-administration and treatment time, of which

Table VII. Correlation of total propofol consumption with age, duration of anaesthesia, body weight, and CCI in cancer patients. †Charlson co-morbidity index. * $p < 0.05$.

Correlation Cancer	Propofol total (mcg/kgBW/min) *vs.* age (n=102)	Propofol total (mcg/kgBW/min) *vs.* duration of anaesthesia (n=103)	Propofol total (mcg/kgBW/min) *vs.* BW (n=103)	Propofol total (mcg/kgBW/min) *vs.* CCI† (n=102)
Spearman r	-0.1293	-0.2254	-2509	-0.1592
95% CI	-0.3211 to -0.07267	-0.4063 to -0.02753	-0.4286 to -0.05455	-0.3482 to -0.04219
p-value	0.1953	**0.0221**	**0.0106**	0.1099
p summary	ns	*	*	ns
Significant? (alfa =0.05)	No	**Yes**	**Yes**	No

Table VIII. Correlation of total propofol consumption with age, duration of anaesthesia, body weight, and CCI in no cancer patients. †Charlson co-morbidity index. ** $p < 0.01$, *** $p < 0.001$.

Correlation No cancer	Propofol total (mcg/kgBW/min) *vs.* age (n=108)	Propofol total (mcg/kgBW/min) *vs.* duration of surgery (n=108)	Propofol total (mcg/kgBW/min) *vs.* BW (n=108)	Propofol total (mcg/kgBW/min) *vs.* CCI† (n=108)
Spearman r	-0.3938	-0.3857	-0.2580	-0.3646
95% CI	-0.5464 to -0.2160	-0.5397 to -0.2068	-0.4308 to -0.06697	-0.5220 to -0.1831
p-value	<0.0001	<0.0001	**0.0070**	**0.0001**
p summary	****	**	**	***
Significant? (alfa =0.05)	**Yes**	**Yes**	**Yes**	**Yes**

significant (negative) correlation was seen only with body weight. However, in contrast to ours, all patients in this study were ASA physical status 1 or 2 and BIS values were targeted in the range of 70-80. Concerning surgery for oncological reasons, Schaefer et al[6] assumed that younger female patients with less co-morbidities received higher propofol dose and had better survival, comparing with older who had more solid cancers and cardiovascular diseases. However, in our patients no significant difference was seen in frequency of co-morbidities between the groups (Table I). The role of age is based on pharmacokinetics of propofol and high hepatic extraction ratio, meaning that propofol elimination is highly dependent on liver perfusion, which ceases when patients get older than 60 years[29,45]. On the other hand, Nunes and co-workers [46] focused on aging brain and loss of gray matter in target organ for propofol effect site. Nevertheless, this cannot explain how age did not affect propofol dose in our cancer patients group. Hence, we considered the ethnicity as a potential cause. In this way, Ortolani et al[33] took into account genetic polymorphisms in the gene encoding liver enzyme cytochrome P450 and epigenetic factors responsible for different sensitivity to propofol, manifested in consumption variability in their studied ethnic groups. It is established that environment and genetics, to some extent, affect the cytochrome CYP2B6 and hydroxylation of propofol in biotransformation process[29]. Importance of the *CYP2B6* gene and c.516G>T polymorphism was explored by Mourão et al[38] on one hundred and eight patients. They revealed that age and presence of T allele had negative association with the total propofol dose. In their study, duration of surgery and weight showed positive predictive correlation, which does not correspond to our results. Furthermore, Zakerska-Banaszak et al[36] in the Polish patients' population also focused on genes coding for the metabolizing enzymes in the liver, cytochromes P-450 2B6 and 2C9, and UDP-glucuronosyl transferase 1A9. According to pharmacokinetic characteristics, they identified three groups of patients, depending on the mean removal time (MRT): rapid (MRT ≤ 30 min), intermediate (100≥MRT>30 min) and poor (MRT>100 min) metabolizers. They suggested

Table IX. Information on regression model using total propofol (ug/kg/min) as dependent variable in no cancer patients. Regression type: least squares. SS – sum of squares of the regression, DF – degrees of freedom, MS – mean square, F – F statistic (MS for the term divided by the MS of the residual). †HTA= hypertension ‡CVD= cardiovascular disease

	Model				
Analysis of variance	SS	DF	MS	F (DFn, DFd)	*p*-value
Regression	25,172	7	3596	F (7, 100) = 4.394	*p*=0.0003
Male	4731	1	4731	F (1, 100) = 5.780	*p*=0.0180
HTA†	411.0	1	411.0	F (1, 100) = 0.5022	*p*=0.4802
Diabetes	242.1	1	242.1	F (1, 100) = 0.2958	*p*=0.5877
Obesity	389.8	1	389.8	F (1, 100) = 0.4763	*p*=0.4917
CVD‡	74.10	1	74.10	F (1, 100) = 0.09054	*p*=0.7641
Age	5478	1	5478	F (1, 100) = 6.694	*p*=0.0111
Body weight	24.18	1	24.18	F (1, 100) = 0.02954	*p*=0.8639
Residual	81,841	100	818.4		
Total	107,014	107			

Table X. Multiple linear regression analysis of variables on predicting total propofol (ug/kg/min) levels in no cancer patients. † HTA=hypertension, ‡CVD= cardiovascular disease, ** $p < 0.05$. $\mathbf{R^2} = 0.2352$.

Parameter estimates	Variable	Estimate	Standard error	95% CI (asymptotic)	ltl	*p*-value
β0	Intercept	135.5	22.13	91.64 to 179.4	6.125	<0.0001****
β1	**Male[1]**	-17.20	7.152	-31.38 to -3.006	2.404	**0.0180 ***
β2	HTA[1] †	-5.666	7.995	-21.53 to 10.20	0.7078	0.4802
β3	Diabetes[1]	4.938	9.078	-13.07 to 22.95	0.5439	0.5877
β4	Obesity[1]	-6.796	9.847	-26.33 to 12.74	0.6902	0.4917
β5	CVD[1] ‡	-2.760	9.174	-20.96 to 15.44	0.3009	0.7641
β6	**Age**	-0.5777	0.2233	-1.021 to -0.1347	2.587	**0.0111 ***
β7	Body weight	-0.05015	0.2918	-0.6291 to 0.5288	0.1719	0.8639

CYP2B6 and ABCB1 variants for further exploration in order to find precise dosing regimen. In the same ethnic group, homozygote c.516T/T in the *CYP2B6* gene was identified more frequently in the rapid metabolizers group. All this, together with the body mass index (BMI), had an impact on propofol metabolism, regardless of the sex[39]. Similarly, in our patients who underwent surgery due to cancers, regression analysis did not show sex to have predictive importance on propofol dose. We might only speculate that higher levels of anxiety in men comparing to women potentially affected propofol dose needed for the desired depth of anaesthesia, as it was reported recently[27,49]. In addition, a recently published study focusing on propofol and cysatracurium sex differences, suggests that ethnicity and geographic location may have importance in dosage calculation of these drugs, in order to achieve optimal effectiveness [35]. We did find weak negative correlation of propofol consumption with body weight and duration of anaesthesia in both groups of patients (Tables VII and VIII). This is not surprising when having in mind high lipophilic property of propofol and increased central compartment volume accompanying higher body mass (BMI) that, in anaesthetic practice, means lower propofol dose with increasing body weight, and vice-versa[28,29,47,48].

Conclusions

Results of our study showed differences in propofol consumption in patients with cancer comparing to no cancer surgery, which is important to have in mind in order to find appropriate dosing regimen for individual patient. We can also speculate that older group of cancer patients might have higher level of anxiety that was not clinically identified, which might explain no difference in propofol dose regarding age in these patients. However, this study opens the way for further research in the field of cancer surgery and specific patients` characteristics. We presume that propofol metabolic pathway could have a role in the different requirement for propofol dose in cancer and no cancer patients, and this hypothesis warrants further exploration. It would be interesting to understand whether potential variation in propofol consumption could be connected with the type of malignancies, planned surgery and patients' characteristics. Finally, in order to find more precise tools for the proper dosing assessment, we believe that further investigations of ethnic peculiarities in the propofol biotransformation route on the broad international scale are of particular importance.

Ethics Statement

Ethics Committee of the Faculty of Medicine in Podgorica (Montenegro) approved the study (No 433/3) on 16.03.2022.

Informed Consent

There were no use of experimental medications or procedures neither patients could be identified, so signed informed consent was waived.

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Authors' Contribution

LjP designed the study, acquired the data, drafted the article and interpreted the data. MŽ analyzed the data, made critical revisions and approved the final version of the article to be published. IĐ helped with the data acquisition.

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Conflict of Interest

All authors declare that they have no conflict of interest.

Data Availability

The datasets analyzed in this study are available from the corresponding author on reasonable request.
References

References

1) Thompson KA, Goodale DB. The recent development of propofol (DIPRIVAN). Intensive Care Med 2000; 26: S400-404.
2) Rüsch D, Arndt C, Eberhart L, Tappert S, Nageldick D, Wulf H. Bispectral index to guide induction of anesthesia: a randomized controlled study. BMC Anesthesiol 2018; 18: 66.
3) Xu Y, Pan S, Jiang W, Xue F, Zhu X. Effects of propofol on the development of cancer in humans. Cell Prolif 2020; 53: e12867.
4) Montejano J, Jevtovic-Todorovic V. Anesthesia and cancer, friend or foe? A narrative review. Front Oncol 2021; 23: 803266.
5) Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery: A retrospective analysis. Anesthesiology 2016; 124: 69-79.
6) Schaefer MS, Raub D, Xu X, Shaydenfish D, Teja B, Chhangani K, Grabitz SD, O'Gara B, Kienbaum P, Houle TT, Landoni G, Eikermann M. Association between propofol dose and 1-year mortality in patients with or without a diagnosis of solid cancer. Br J Anaesth 2020; 124: 271-280.
7) Zhang J, Chang CL, Lu CY, Chen HM, Wu SY. Long-term oncologic outcomes of breast conserving surgery with propofol-based total intravenous anesthesia or volatile inhalational general anesthesia without propofol: a propensity score-matched, population-based cohort study. Am J Cancer Res 2021; 11: 4966-4980.
8) Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, Wong CS, Wu ZF. Propofol-based total intravenous anesthesia did not improve survival compared to desflurane anesthesia in breast cancer surgery. PLoS One 2019; 14: e0224728.
9) Oh TK, Kim HH, Jeon YT. Retrospective analysis of 1-year mortality after gastric cancer surgery: Total intravenous anesthesia versus volatile anesthesia. Acta Anaesthesiol Scand 2019; 63: 1169-1177.
10) Hong B, Lee S, Kim Y. Lee M, Youn AM, Rhim H, Hong S-H, Kim Y-H, Yoon S-H, Lim Ch. Anesthetics and long-term survival after cancer surgery—total intravenous versus volatile anesthesia: a retrospective study. BMC Anesthesiol 2019; 19:233.
11) Enlund M, Berglun A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic—sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis. Upsala J Med Sci 2014; 119: 251-261.
12) Zhang L, Wang N, Zhou S, Ye W, Jing G, Zhang M. Propofol induces proliferation and invasion of gallbladder cancer cells through activation of Nrf2. J Exp Clin Cancer Res 2012; 31: 66.
13) Meng C, Song L, Wang J, Li D, Liu Y, Cui X. Propofol induces proliferation partially via downregulation of p53 protein and promotes migration via activation of the Nrf2 pathway in human breast cancer cell line MDA-MB-231. Oncol Rep 2017; 37: 841-848.
14) Tseng W-C, Lee M-S, Lin Y-C, Lai H-C, Yu M-H, Wu K-L and Wu Z-F. Propofol-Based Total Intravenous Anesthesia is Associated with Better Survival than Desflurane Anesthesia in Epithelial Ovarian Cancer Surgery: A Retrospective Cohort Study. Front Pharmacol 2021; 12: 685265.
15) Su Z, Liu HL, Qi B, Liu Y. Effects of propofol on proliferation and apoptosis of cardia cancer cells via MAPK/ERK signaling pathway. Eur Rev Med Pharmacol Sci 2020; 24: 428-433.
16) Ishikawa M, Iwasaki M, Sakamoto A, Ma D. Anesthetics may modulate cancer surgical outcome: a possible role of miRNAs regulation. BMC Anesthesiol 2021; 21: 71.
17) Taniguchi T, Kanakura H, Yamamoto K. Effects of posttreatment with propofol on mortality and cytokine responses to endotoxin-induced shock in rats. Crit Care Med 2002; 30: 904-907.
18) Ke JJ, Zhan J, Feng XB, Wu Y, Rao Y, Wang YL. A comparison of the effect of total intravenous anaesthesia with propofol and remifentanil and inhalational anaesthesia with isoflurane on the release of pro- and anti-inflammatory cytokines in patients undergoing open cholecystectomy. Anaesth Intensive Care 2008; 36: 74-78.
19) O'Bryan LJ, Atkins KJ, Lipszyc A, Scott DA, Silbert BS, Evered LA. Inflammatory Biomarker Levels After Propofol or Sevoflurane Anesthesia: A Meta-analysis. Anesth Analg 2022; 134: 69-81.
20) Maeda S, Tomoyasu Y, Higuchi H, Honda Y, Ishii-Maruhama M, Miyawaki T. Female patients require a higher Propofol infusion rate for sedation. Anesth Prog 2016; 63: 67-70.
21) Riphaus A, Slottje M, Bulla J, Keil C, Mentzel Ch, Limbach V, Schultz B, Unzicker C. Women awaken faster than men after electroencephalogram-monitored propofol sedation for colonoscopy: A prospective observational study. Eur J Anaesthesiol 2017; 34: 681-687.
22) Haensch K, Schultz A, Krauss T, Grouven U, Schultz B. Women need more propofol than men during EEG-monitored total intravenous anaesthesia. Biomed Tech (Berl) 2009; 54: 76-82.
23) Loryan I, Lindqvist M, Johansson I, Hiratsuka M, van der Heiden I, van Schaik RH, Jakobsson J, Ingelman-Sundberg M. Influence of sex on propofol metabolism, a pilot study: implications for propofol anesthesia. Eur J Clin Pharmacol 2012; 68: 397-406.
24) Choong E, Loryan I, Lindqvist M, Nordling Å, el Bouazzaoui S, van Schaik RH, Johansson I, Jakobsson J, Ingelman-Sundberg M. Sex difference in formation of propofol metabolites: a replication study. Basic Clin Pharmacol Toxicol 2013; 113: 126-131.
25) Pleym H, Spigset O, Kharasch ED, Dale O. Gender differences in drug effects: implications for

anesthesiologists. Acta Anaesthesiol Scand 2003; 47: 241-259.
26) Choi JJ, Kim JY, Lee D, Chang YJ, Cho NR, Kwak HJ. Male patients require higher optimal effect-site concentrations of propofol during i-gel insertion with dexmedetomidine 0.5 μg/kg. BMC Anesthesiol 2016; 16: 20.
27) Uysal AI, Altıparmak B, Toker MK, Dede G, Sezgin Ç, Demirbilek SG. The effect of preoperative anxiety level on mean platelet volume and propofol consumption. BMC Anesthesiol 2020; 20: 34.
28) Johnson AL, Altshuler D, Schwartz DR, Papadopoulos J. Effect of obesity on propofol dosing requirements in mechanically ventilated patients in a medical intensive care unit. J Emerg Crit Care Med 2018; 2: 97.
29) Sahinovic MM, Struys MMRF, Absalom AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. Clin Pharmacokinet 2018; 57: 1539-1558.
30) Delfino AE, Cortinez LI, Fierro CV, Muñoz HR. Propofol consumption and recovery times after bispectral index or cerebral state index guidance of anaesthesia. Br J Anaesth 2009; 103: 255-259.
31) Zarei S, Costas Y, Orozco G, Zaydlin M, Mirtar A, Abouali M, Diaz-Marty C, Akhlaghipour G, Fernandez Altamirano P, Gonzalez Cardona AR, Reiley LE, Mirzakhani H. A Web-Based Pharmacogenomics Search Tool for Precision Medicine in Perioperative Care. J Pers Med 2020; 10: 65.
32) Jhun EH, Apfelbaum JL, Dickerson DM, Shahul S, Knoebel R, Danahey K, Ratain MJ, O'Donnell PH. Pharmacogenomic considerations for medications in the perioperative setting. Pharmacogenomics 2019; 20: 813-827.
33) Ortolani O, Conti A, Chan YK, Sie MY, Ong GS. Comparison of propofol consumption and recovery time in Caucasians from Italy, with Chinese, Malays and Indians from Malaysia. Anaesth Intensive Care 2004; 32: 250-255.
34) Campesi I, Montella A, Seghieri G, Franconi F. The Person's Care Requires a Sex and Gender Approach. J Clin Med 2021; 10: 4770.
35) Dahaba AA, Xiao Z, Zhu X, Oettl K, Dong H, Xiong L, Zelzer S, Zhao S, Reibnegger G. Location matters: Overlooked ethnic-geographic effect in China and Austria on propofol/cisatracurium sex differences among a population pharmacokinetic/pharmacodynamic (PopPK/PD) covariate analysis in men, women, and one transgender subject. Fundam Clin Pharmacol 2022; 36: 182-198.
36) Zakerska-Banaszak O, Skrzypczak-Zielinska M, Tamowicz B, Mikstacki A, Walczak M, Prendecki M, Dorszewska J, Pollak A, Lechowicz U, Oldak M, Huminska-Lisowska K, Molinska-Glura M, Szalata M, Slomski R. Longrange PCR-based next-generation sequencing in pharmacokinetics and pharmacodynamics study of propofol among patients under general anaesthesia. Sci Rep 2017; 7: 15399.
37) Mikstacki A, Zakerska-Banaszak O, Skrzypczak-Zielinska M, Tamowicz B, Prendecki M, Dorszewska J, Molinska-Glura M, Waszak M, Slomski R. The effect of UGT1A9, CYP2B6 and CYP2C9 genes polymorphism on individual differences in propofol pharmacokinetics among Polish patients undergoing general anaesthesia. J Appl Genet 2017; 58: 213-220.
38) Mourão AL, de Abreu FG, Fiegenbaum M. Impact of the Cytochrome P450 2B6 (CYP2B6) Gene Polymorphism c.516G>T (rs3745274) on Propofol Dose Variability. Eur J Drug Metab Pharmacokinet 2016; 41: 511-515.
39) Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, Balch C, Brennan MF, Dare A, D'Cruz A, Eggermont AM, Fleming K, Gueye SM, Hagander L, Herrera CA, Holmer H, Ilbawi AM, Jarnheimer A, Ji JF, Kingham TP, Liberman J, Leather AJ, Meara JG, Mukhopadhyay S, Murthy SS, Omar S, Parham GP, Pramesh CS, Riviello R, Rodin D, Santini L, Shrikhande SV, Shrime M, Thomas R, Tsunoda AT, van de Velde C, Veronesi U, Vijaykumar DK, Watters D, Wang S, Wu YL, Zeiton M, Purushotham A. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. Lancet Oncol 2015; 16: 1193-1224.
40) Romito B, Stone J, Ning N, Yin C, Llano EM, Liu J, Somanath K, Lee CT, Matchett G. How Drug Shortages Affect Clinical Care: The Case of the Surgical Anesthetic Propofol. Hosp Pharm 2015; 50: 798-805.
41) Kreuer S, Schreiber JU, Bruhn J, Wilhelm W. Impact of patient age on propofol consumption during propofol–remifentanil anaesthesia. Eur J Anaesthesiol 2005; 22: 123-128.
42) Eleveld DJ, Proost JH, Cortínez LI, Absalom AR, Struys MM. A general purpose pharmacokinetic model for propofol. Anesth Analg 2014; 118: 1221-1237.
43) Chan SM, Lee MS, Lu CH, Cherng CH, Huang YS, Yeh CC, Kuo CY, Wu ZF. Confounding factors to predict the awakening effect-site concentration of propofol in target-controlled infusion based on propofol and fentanyl anesthesia. PLoS One 2015; 10: e0124343.
44) Vuyk J, Oostwouder CJ, Vletter AA, Burm AG, Bovill JG. Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion. Br J Anaesth 2001; 86: 183-188.
45) Hiraoka H, Yamamoto K, Miyoshi S, Morita T, Nakamura K, Kadoi Y, Kunimoto F, Horiuchi R. Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. Br J Clin Pharmacol 2005; 60: 176-182.
46) Nunes CS, Ferreira DA, Antunes L, Lobo F, Santos IA, Amorim P. Individual effect-site concentrations of propofol at return of consciousness are related to the concentrations at loss of consciousness and age in neurosurgical patients. J Clin Anesth 2009; 21: 3-8.
47) Araújo AM, Machado HS, Falcão AC, Soares-da-Silva P. Reliability of body-weight scalars on the assessment of propofol induction dose in obese patients. Acta Anaesthesiol Scand 2018; 62: 464-473.
48) Erstad BL, Barletta JF. Drug dosing in the critically ill obese patient-a focus on sedation, analgesia, and delirium. Crit Care 2020; 24: 315.
49) Yilmaz Inal F, Yilmaz Camgoz Y, Daskaya H, Kocoglu H. The Effect of Preoperative Anxiety and Pain Sensitivity on Preoperative Hemodynamics, Propofol Consumption, and Postoperative Recovery and Pain in Endoscopic Ultrasonography. Pain Ther 2021; 10: 1283-1293.