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ORIGINAL RESEARCH

A Prospective Study on Severe Hypotension in Critically Ill Patients Sedated with Propofol

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Abstract

Background: We aimed to verify if mean arterial pressure (MAP) at initiation of Propofol infusion and the APACHE score can predict the risk of severe hypotension.

Methods: A prospective study on 100 patients treated with Propofol during their stay at the Main University Hospital between 2017 and 2018. We estimated relative risks (RRs) of severe hypotension according to MAP and APACHE score categories using a modified Poisson model for binary outcome.

Results: Fifty-three patients developed severe hypotension. Compared to patients with MAP ≥ 100 mmHg, the RR were: 3.59 (95% CI: 1.68; 7.67) for patients with MAP between 80 and 100 mmHg and 5.28 (95% CI: 2.48; 11.21) for patients with MAP < 80. Patients with APACHE II score between 10-15 had a RR of 4.00 (95% CI: 2.11; 7.59) compared to patients with APACHE score below 10 points. The RR was 4.83 (95% CI: 2.65; 8.80) for those with APACHE II score > 15 points.

Conclusion: Clinicians should use Propofol with caution in patients having low baseline MAP and high APACHE score.

Keywords

Propofol, Hypotension, Human, Critical illness, Prospective studies, Sedatives

Introduction

Propofol is a short acting, intravenously administrated hypnotic/amnestic agent. Propofol is one of the most common drugs used in sedation in critically ill patients due to its pharmacological properties, which allow serial neurological examination during treatment. It is used in initiation and maintenance of general anesthesia, sedation for mechanically ventilated patients and procedural sedation [1].

The duration of Propofol clinical effect is short, because it is rapidly distributed into peripheral tissues. When used for IV sedation, a single dose of Propofol typically wears off within minutes [2].

Propofol exerts its action through a Gamma amino butyric acid (GABA) receptor interaction; GABA is the principle inhibitory neurotransmitter in the central nervous system (CNS) [3]. Diminishing cerebral blood flow, cerebral metabolic oxygen consumption and intracranial pressure are also characteristic of Propofol administration [4]. One of its common side effects is hypotension which occurs in incidence as high as 68% [5,6]. Development of hypotension during intensive care unit (ICU) stay has been shown to increase mortality and unfavorable outcomes [7,8].

The Acute Physiology and Chronic Health Evaluation (APACHE II) is a severity score tool commonly used in ICU patients, also to estimate mortality risk [9].

We hypothesised that low mean arterial pressure and high APACHE scores are risk factors for the development of severe hypotension at initiation of Propofol infusion.

Materials and Methods

A prospective study was conducted on 100 adult

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patients consecutively admitted to the critical care medicine department in the Main University Hospital between January 1, 2017 and February 29, 2018. All selected patients were on Propofol infusion for more than 4 hours. Exclusion criteria were: Sedation for any procedure, vasopressor initiation before start of sedation, history of heart block and pregnant women.

Observational end points were the development of severe hypotension, discharge, death or until 100 data sets were completed.

Blood pressure was measured by two different nurses to ensure that all eligible patients were free from severe hypotension (primary outcome) at beginning of the study. Nurses who assessed patients and recorded vital signs were blinded to the study objective to minimize information bias.

Collected data included patients demographic characteristics as age and gender, diagnosis on admission, Glasgow Coma Scale (GCS) on admission, APACHE II score, indication of Propofol infusion, MAP, heart rate at initiation of infusion, Propofol infusion rate, ejection fraction estimated by echocardiography, hypoxic index, serum bicarbonate, medical history (diabetes mellitus, hypertension, congestive heart failure, atrial fibrillation,

Table 1: Comparison between normotensive and hypotensive patients according to demographic characteristics, propofol infusion, diagnosis on admission and past medical history.

	Normotensive (n = 47)	Hypotensive (n = 53)	Unadjusted RR (95% CI)	P value
Age (years)	37.3 (14.6)	52.0 (17.1)	1.02 [1.01;1.04]	< 0.001
Female, n *(%)*	15 (31.9)	30 (56.6)	1.59 [1.09;2.31]	0.035
Weight (kg)	83.6 (11.5)	78.9 (12.4)	0.98 [0.96;1.01]	0.049
Indication of Propofol infusion				
Sedation on MV	35 (74.4)	37 (69.8)	0.92 [0.5;1.70]	0.66
Convulsions	15 (31.9)	13 (24.5)		
Rate of propofol infusion (µg/kg/min), *median (25^{th} - 75^{th})*	26.0 (5.0)	25.0 (9.0)	0 [0;2.e+12]	0.6
Heart rate (beat/min)	90 (13.2)	90 (10)	0.96 [0.76;1.2]	0.12
Hypoxic index	231.27 (77.63)	170.09 (53.02)	0.99 [0.99;1]	< 0.001
Serum Creatinine (mg/dl)	0.979 (0.235)	2.41 (1.97)	1.19 [1.06;1.33]	< 0.001
Bicarbonate (mlEq/L)	21.5 (4.7)	17.35 (3.58)	0.9 [0.84;0.96]	< 0.001
Diagnosis on admission, *n (%)*				
Traumatic brain injury	19 (40.4)	1 (1.8)	0.08 [0.01;0.056]	< 0.001
Intracranial Hemorrhage	16 (34.0)	11 (20.7)	0.66 [0.33;1.32]	0.13
Status epileptics	12 (25.5)	11 (20.7)	0.87 [0.44;1.74]	0.55
Heart failure	1 (2.1)	4 (7.5)	1.55 [0.56;4.3]	0.35
Respiratory failure	12 (25.5)	21 (39.6)	1.35 [0.77;2.35]	0.15
Severe sepsis	0	26 (49.05)	2.68 [1.56;4.59]	< 0.001
Burn	3 (6.3)	4 (7.5)	1.28 [0.46;3.54]	1.00
Snake bite	0	1 (1.8)	1.9 [0.26;13.77]	1.00
APACHE II score	7.7 (3.4)	14.7 (5.6)	1.08 [1.04;1.13]	< 0.001
MAP at initiation of propofol infusion	104 (11)	87 (12)	0.96 [0.94;0.98]	< 0.001
RRT need n (%)	0	14 (26.4)	2.15 [1.13;4.08]	0.002
Past medical history, *n (%)*				
Diabetes	11 (23.4)	26 (49.05)	1.37 [0.98 to 1.93]	0.05
Hypertension	12 (25.5)	20 (37.7)	1.29 [0.74;2.24]	0.21
Chronic Congestive heart failure	1 (2.1)	5 (9.4)	1.63 [0.65;4.10]	0.21
Atrial fibrillation	0	6 (11.3)	2.0 [1.63 to 2.44]	0.029
Acute kidney injury	0	23 (43.3)	2.57 [1.48;4.45]	< 0.001
End stage renal disease	0	7 (13.2)	2.02 [1.64 to 2.48]	0.014
Liver cirrhosis	2 (4.2)	9 (16.9)	1.65 [1.16 to 2.34]	0.042

MAP: Mean Arterial Pressure; RRT: Renal Replacement Therapy.

cardiovascular surgery, cirrhosis, acute kidney injury, end stage renal disease) and serum creatinine.

Primary outcome was the development of severe hypotension, defined as a mean arterial pressure below 60 mmHg while on Propofol infusion. We chose this definition to ensure that we recorded a side effect of Propofol infusion not hemodynamic variability commonly seen in the ICU patients.

We collected 100 patients based upon the hypothesis of rule of thumb for sample size calculation in a reliable regression model to predict severe hypotension outcome "10-15 cases of data for each predictor in the model" [10].

We used Student's t-test to compare continuous variables between patients who developed hypotension and those who did not, while for categorical variables we used Pearson's chi-squared test or Fisher exact test (if at least one expected cell count was below 5).

We conducted a univariate analysis. Among large number of statistically significant predictors, we selected variables that were both statistically significant and clinically important to be included in our model. The relative risks (RRs) and 95% confidence intervals (CIs) for hypotension were estimated by modified Poisson regression models for binary data with robust error variance [11]. This model is more advantageous than logistic regression as RR is easily interpreted. In addition, unlike odds ratio, the adjusted RR is not overestimated in our case of common event rate. (53% hypotension).

The model for MAP included age category (< 45, 45-64 and ≥ 45 years), MAP category (< 80, 80-99 and ≥ 100 mmHg) and need for renal replacement therapy (Yes/No). We couldn't include more than 3 up to 4 variables in the model to preserve the power of the model. Need for renal replacement therapy (RRT) was included in the model since it had been associated with increased risk of hypotension during Propofol infusion [12]. Patients the RRs for APACHE II score were estimated separately to avoid multicollinearity problems. In fact, age, MAP and end-stage renal disease are all among the issues of the APACHE II score [9]. APACHE II score was included in the model as categorical variable (< 10, 10-14 and ≥ 15 points. Statistical analysis was done using R software. All statistical tests are two tailed at 0.05 significance level.

Results

We included 100 patients for our study. Of them, 53 developed hypotension while in propofol therapy. No patient died during the follow-up.

Table 1 shows demographics and clinical characteristics of the hypotensive and normotensive patients at the beginning of Propofol infusion. Indication for Propofol infusion and mean rate of infusion did not differ significantly between hypotensive and normotensive patients. Hypotensive patients were older (P < 0.001) than normotensive patients, and they had higher APACHE II score (P < 0.001) and lower MAP (P < 0.001) at initiation of Propofol infusion. The mean hypoxic index and serum bicarbonate were significantly higher among hypotensive patients (P < 0.001), while they recorded significantly higher mean serum creatinine relative to normotensive patients (P < 0.001). The frequency of traumatic brain injury (38% *vs.* 2%) and severe sepsis (0 *vs.* 46%) was higher in hypotensive than in normotensive patients, as well as the proportion of patients who needed renal replacement therapy (0% *vs*. 25%).

Table 2: Incidence of hypothension according to age, mean arterial pressure and APACHE score categories.

	Hypotensive/ All patients	% of all patients
Age, years		
19-44	15/47	31.9
45-64	27/40	67.5
65-80	11/13	84.6
MAP, mmHg		
63-79	10/10	100
80-99	38/55	69.1
100-133	5/30	14.3
Need for Renal Replacement Therapy (RRT)		
No	41/88	46.6
Yes	12/12	100
APACHEII score		
2-9	9/48	18.8
10-14	15/20	75.0
15-30	29/32	90.6

Regarding past medical history; atrial fibrillation (AF), acute kidney injury (AKI) and cirrhosis were more frequent in the hypotensive group (P = 0.029, p < 0.001 and P = 0.042 respectively) and borderline significance was observed for history of diabetes mellitus (DM) in hypotensive than normotensive patients (P = 0.05).

Table 2 gives the incidence of hypotension according to age, MAP and APACHEII score categories, and for patients who needed RRT. The risk of hypotension was higher in older patients and in those with high APACHE score, while it increased with decreased MAP.

Table 3 gives the estimates of the RRs for each stratum of age, MAP and APACHE score category. Patients with MAP below 80 mmHg had 5.8-fold increase in the risk of hypotension than patients with MAP higher or equal to 100 mmHg. Likewise, patients with APACHE score higher than 15 had a 4.8-fold increase in the risk of hypotension compared to patients with APACHE score below 10.

Discussion

IV Propofol is commonly used for continuous seda-

Table 3: Relative risk (RR) of hypothension during propofol infusion according to age, mean arterial pressure (MAP), need for renal transplantation and APACHEII score.

Model 1	**RR [95% CI]** [a]
Age, 19-44 years	[12]
Age, 45-64 years	2.07 [1.30; 3.29]
Age, 65-80 years	3.05 [1.85; 5.02]
MAP, 100-133 mmHg	[12]
MAP, 63-79 mmHg	5.28 [2.48; 11.21]
MAP, 80-99 mmHg	3.59 [1.68; 7.67]
RRT	
No	[12]
Yes	2.79 [1.77; 4.41]
Model 2	
APACHEII score, 2-9 points	[12]
APACHEII score, 10-14 points	4.00 [2.11; 7.59]
APACHEII score, 15-30 points	4.83 [2.65; 8.80]

[a]Relative risks and 95% Confidence intervals were estimated by Poisson models with robust error variance; Model 1 included age, MAP and RRT; whereas Model 2 included APACHEII score.

tion in ICU patients. However, it is also administered as interrupted bolus doses [6]. Pharmacokinetics properties of Propofol are advantageous for fast onset, rapid awakening with little drug accumulation especially with interrupted bolus doses that commonly occurs in patients with hepatic and renal dysfunction [13]. Propofol hazards are smaller compared to benzodiazepines which make it the drug of choice for continuous sedation [13]. Compared with midazolam, Propofol allows for better manipulation of the level of sedation, thereby adjusting sedation to patient condition [14]. However, a common adverse effect is the occurrence of hypotension with Propofol, which necessitates the study of potential predictors to avoid concomitant complications among ICU patients, administrated IV Propofol [15]. In our study, patients aged more than forty-five years with baseline MAP < 100 and APACHE II score > 10 were independently associated with severe hypotension.

Around half of the included patients developed severe hypotension on IV Propofol infusion. Other studies have reported high incidence of Propofol derived hypotension [16,17]. In a randomized prospective study, 68% of Propofol patients versus 31% of midazolam patients had a > 20% decrease in systolic blood pressure after the loading dose [16]. A British study concluded that Propofol tripled the risk of hypotension among critically ill patients and were at higher risk of requiring a vasopressor to treat hypotension [17]. On the other hand, a lower incidence was conversely reported in a prospective, double-blind, open-label, randomized study in USA with 9.8% and 17.4% incidence of hypotension for Propofol and midazolam sedated patients respectively [18]. Another study reported a lower hypotension incidence of 26% compared to our study [19]. The incidence variability could be explained by variable definition of hypotension used in other studies may have led to higher [16,18] or lower [20,21] incidences and may also be due to method and rate of initial administration.

Age was independently associated with severe hypotension both in univariate and multivariate analyses. In concordance with our findings, a study found that 50% of patients sedated with Propofol experienced hypotension with increasing incidence in those > 60 years of age [22]. Another study from Taiwan concluded that age is the strongest risk factor for hypotension and Propofol should be given with caution in elderly hospitalized patients [23]. Possible mechanisms are combined decrease in vascular resistance and cardiac output as consequence of arterial, venous vasodilatation and diminished myocardium contraction after Propofol infusion in elderly patients [24].

We specifically selected APACHE II score for inclusion in our model as an independent predictor for hypotension. In agreement with our study, a study from the USA, median APACHE II score was significantly higher among the hypotensive patients [12]. The advantage of this score that its calculation is early feasible upon patient admission to ICU [25]. It is convenient and can be used to predict wide ranges of outcomes as in trauma [26] and sepsis [27], not only hypotension in critically ill patients. Our study is consistent with the conclusion of a study for APACHE II score as an indicator of illness severity and predictor of mortality/neurologic morbidity within 72 hours after admission [25]. Previous studies rarely assessed the independent association between high APACHE II score and occurrence of hypotension [12].

The five-fold increase risk of hypotension among patients with a MAP below 80 mmHg was supported by a study with baseline MAP (60-70 mmHg) at the start of infusion [12]. Many studies concluded that Propofol causes both venous and arterial vasodilatation [28], potentially resulting in increased risk of hypotension in patients with a lower MAP at baseline [29,30]. Others have postulated that judicious administration of IV fluids to replace intravascular volume may lower the incidence of hypotension [29]. A study of patients undergoing intubation demonstrated that Peri-operative volume loading aided in maintaining hemodynamic stability, with those who received fluid boluses experiencing a lower rate of hypotension 10-min post Propofol administration [31].

In our study, around three-fold increase risk of hypotension among patients on RRT. This is consistent with another study that reported a 12-fold increased risk of hypotension during RRT [12]. We specifically included RRT in the model because patients on RRT had also elevated serum creatinine and bicarbonate that were proved to be associated with increased risk of hypotension. The mechanism of hypotension may be explained

by decrease intravascular volume [12]. Also, patients who need dialysis usually undergo the conventional methods of RRT which are commonly associated with hypotension [32].

We didn't include weight as it is well known that overweight is a risk factor for hypertension rather than hypotension [33]. Sepsis and acute kidney injury were important domains used to calculate APACHE II score which can substitute these variables for inclusion in the model.

So, we closely inspected APACHE II score but no other significant predictors to include this comprehensive score illustrating many items simultaneously instead of addressing the contribution of individual predictors [9,25]. Upon patient admission to ICU, all chronic conditions including DM are controlled through routine patient management that's why we didn't include DM in the model. Little studies assessed the association between isolated brain injury and Propofol-induced hypotension. One study revealed that most patients with isolated head injuries are associated with normal blood pressure with little skewness towards high blood pressure [34].

Conclusion

Propofol is associated with severe hypotension in the context of high APACHE II score, renal replacement therapy, age and initial MAP of less than 80. Therefore, we recommend, we recommend slow and progressive dose titration of IV Propofol among patients > 45 years. Clinicians should consider restricting or at least close monitoring of Propofol in patients with APACHE II score > 10 and baseline MAP < 100.

Potential Conflict of Interest

The authors declare that they have no conflict of interest.

Role of Authors

Sherif Abdelmonem: Clinical input and approval of the final modifications before submission; Tamer A Helmy: Clinical input and approval of the final modifications before submission; Iman El Sayed: Manuscript edition, writing and statistical analysis; Salma Ghazal: Data collection.

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