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Research Article

Comparative Study of Oxytocin on Hemodynamic Parameters in Variceal Upper Gastrointestinal Bleeding in Antananarivo

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Abstract

Introduction

Variceal upper gastrointestinal bleeding remains a common pathology, particularly in Madagascar, because of its schistosomiasis and cirrhotic etiology. It remains an important cause of morbidity and mortality, especially since the vasoactive treatment or the band ligation are not performed early. In Madagascar, vasoactive drugs (octreotide, somatostatin, terlipressin) are unavailable. In the Surgical Intensive Care Unit of the JR Andrianavalona University Hospital Center (CHU JRA), before 2015, oxytocin was used as an "alternative" for vasoactive treatment. The aim of this study was to assess the effect of oxytocin on hemodynamic parameters and to compare them according to the use or not use of oxytocin in variceal upper gastrointestinal bleeding.

Method

Case - control study was performed in the Surgical Intensive Care Unit of CHU JRA over eight

years (from 2010 to 2017). The study population was divided into two groups: O+ Group (use of oxytocin, from 2010 to 2014) and O- Group (no use of oxytocin, from 2015 to 2017). The demographic, hemodynamic parameters of patients with variceal upper gastrointestinal bleeding were studied. The comparison (Mann Whitney test) of the hemodynamic parameters according to the use of oxytocin between the two groups and the correlations (Pearson's test) between the use of oxytocin and the hemodynamic parameters as well as the mortality were analyzed (SIGMASTAT® 3.5).

Results

Total 269 patients (47.1 ± 13.7 years, mostly male, sex ratio = 2.53) were used for this study. Oxytocin was administered intraveinously to 175 patients in the O+ group versus (vs) 94 patients in the O- group (in whom oxytocin has not been administered). Systolic blood pressure (98.5 ± 7.5 vs 100.3 ± 24.3mmHg), heart rate (73 ± 13.7 vs 77.5 ± 8.7bpm) and shock index (0.7 ± 0.23 vs 0.7 ± 0.1) were not correlated with the use of oxytocin and were similar in both groups. The mean arterial pressure was 69 ± 5.6 vs 72.4 ± 7.8 mmHg [p = 0.026 (Mann Whitney test)]; with oxytocin having a significant impact [R = 0.33 (Pearson test correlation), p = 0.0237). Mortality was not correlated with the use of oxytocin (18.3% vs 11.7%).

Conclusion

The management of variceal upper gastrointestinal bleeding relies, among other things, on the optimization of mean arterial pressure. Oxytocin has cardio-vascular properties, which could thus, act on this parameter without impact on mortality. Although the results show an impact of oxytocin on the mean arterial pressure, this molecule could be interesting until the vasoactive molecules are available in Madagascar.

Abbreviations

CHU-JRA : Centre Hospitalier Universitaire Joseph Ravoahangy Andrianavalona
DH : Digestive Hemorrhage
HR : Heart Rate
MAP : Mean Arterial Pressure
OT : Oxytocin
SBP : Systolic Blood Pressure
SI : Shock Index
UGIB : Upper Gastrointestinal Bleeding
VUGIB : Variceal Upper Gastrointestinal Bleeding

Introduction

Any gastrointestinal bleeding (GIB) occurring in a patient with portal hypertension is a frequent reason for admission to intensive care and resuscitation [1]. It represents a major therapeutic emergency that requires

multidisciplinary management [1]. Despite of recent progress [vasoactive treatment, band ligations, transjugular intrahepatic portosystemic shunt (TIPS)],variceal upper gastrointestinal bleeding (VUGIB) in the cirrhotic patients remains burdened with very high mortality [2].

Hepatic schistosomiasis can also be complicated by portal hypertension with variceal rupture for complication. The emergency treatment of VUGIB of portal hypertension in schistosomiasis has no particularity and is based on medical treatment (beta blockers), variceal sclerosis or band ligation, and surgical treatment (splenectomy) [3]. In cirrhotic patients, increased intrahepatic vascular resistance and portal flow contribute to the development of portal hypertension. Treatment includes general measures, common to all digestive hemorrhages and specific measures to cirrhosis and schistosomiasis [4, 5]. Four types of specific treatments can be proposed, administered alone or in combination: vasoactive drugs, endoscopic techniques, balloon tamponade and portosystemic derivations [6]. The goal of drug treatments is to stop bleeding by reducing blood flow and intravascular pressure leading to haemostasis at the bleeding site. Vasoactive treatment (somatostatin, terlipressin or octreotide) should be initiated early, indeed as soon as possible and systematically. This treatment can be used alone or in combination with an endoscopic technique; its advantage is the immediate availability and ease of use [7,8]. But these drugs are not yet available in Madagascar. However, for a period of time – before 2015 -, it was observed that oxytocin was used in the treatment of variceal upper gastrointestinal bleeding in the absence of these vascoactive drugs in the surgical intensive care unit of CHU JRA (Centre Hospitalier Universitaire JR Andrianavalona). Thus, a study in patients admitted for varicose rupture, analyzing the influence of oxytocin on the hemodynamic status was performed. The main objective was to compare the effect of this molecule on the hemodynamic parameters, according to the period of use (before and after 2015); then to study the correlations between oxytocin use and hemodynamic parameters [systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR) and shock index (SI)].

Methods

A retrospective, comparative study was conducted in the surgical intensive care unit at the Joseph Ravoahangy Andrianavalona University Hospital Center (CHU JRA) over a period of eight years (from January 2010 to December 2017). Inclusion criteria were patient records, presenting with upper gastrointestinal bleeding, whose variceal origin was suspected before history data, specific clinical signs of portal hypertension and / or confirmed by upper gastrointestinal endoscopy. All records of these patients were considered, with or without therapy with oxytocin (10 to 15 IU administered by continuous infusion) in the case of high varicose gastrointestinal bleeding. Since the use of oxytocin extended from January 2010 to December 2014, the study population was divided in two: O+ group (patients who received oxytocin during hospitalization, before the year 2015) and O- group (patients who have not received oxytocin since the year 2015). The criteria for non-inclusion were the records of patients admitted for gastrointestinal bleeding whose varicose origin was not suspected. Exclusion criteria were upper digestive hemorrhage where endoscopy did not reveal digestive varices.

The primary endpoint was the hemodynamic parameters of the patients.

The studied parameters were demographic parameters (including age, gender and prior pathologies); the reason for admission (hematemesis, melena or both); hemodynamic parameters [systolic arterial blood

pressure (SBP), mean arterial pressure (MAP), heart rate (HR) and shock index (SI)]; the medical management and the outcome of patients.

Statistical analysis was performed with the SIGMASTAT® 3.5 software. The results are expressed as a percentage for the qualitative variables and on average with standard deviation for the quantitative variables. The Mann Whitney comparison test and the Pearson correlation test were used for statistical analysis on oxytocin use and hemodynamic parameters as well as mortality. A value of p less than 0.05 is considered significant.

Results

Over a period of eight years, 269 cases of upper gastrointestinal bleeding, with varicose origin, were studied, which represented 1.4% of admissions in the unit and 14% of digestive hemorrhages during the study period (Figure 1). Among the 269 patients includes, 175 (65%) patients received oxytocin intraveinously (O+ group) and 94 (35%) patients didn't receive any oxytocin (O- group).

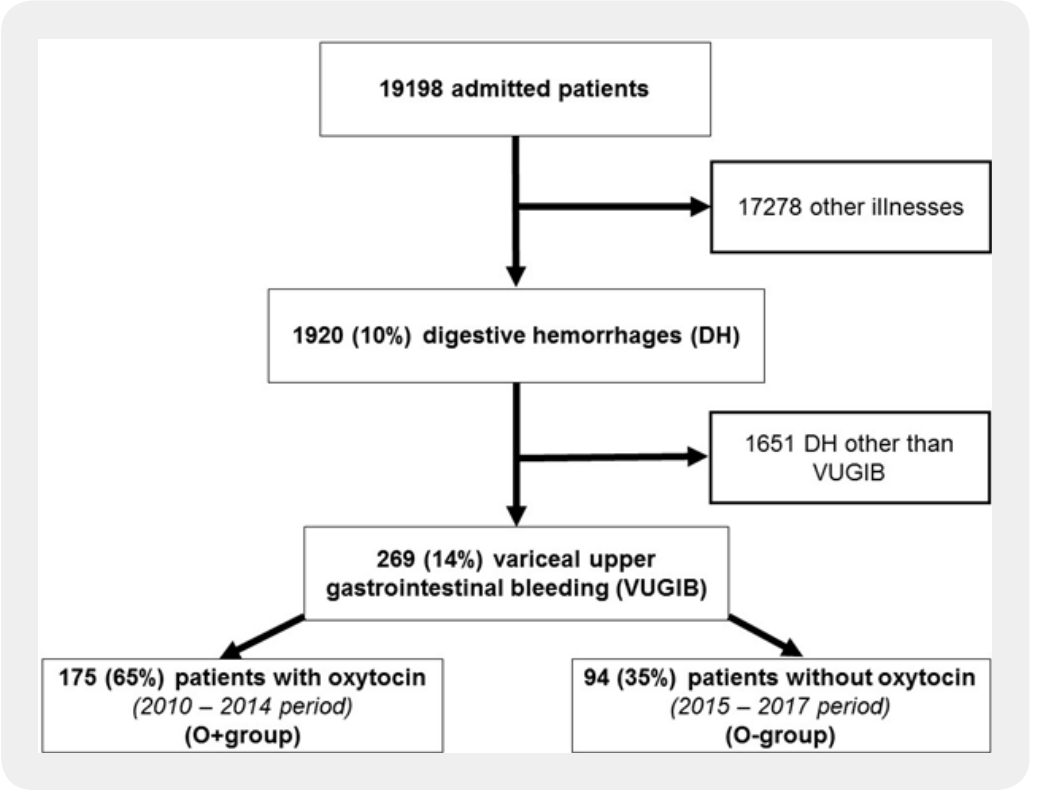


Figure 1: *Population Study*

In this study, the population was mostly male with a sex ratio of 2.44. Patients' ages ranged from 22 to 81 years, with an average of 47.1 ± 13.3 years. Admissions in the unit were mainly hematemesis and melena (56.1%) (Table 1). About the antecedents, 34 patients (19.4%) had a history of esophageal varices in the O+ group versus 18.1% in O-group; and prior band ligation (14.9%) and toxic habits (alcohol and tobacco: 27.7%) were more important in the O- group than in the O+ group (Table 2). The dose of oxytocin used ranged from 10 to 15 IU, administrated by continuous intravenous infusion for 24 hours (in O+ group); the average dose of oxytocin administered was 11.2 ± 2.5 IU. This molecule was used as soon as the patients were admitted in the unit, until the tenth / twelfth day of hospitalization.

Table 1: *Characteristics of the study population*

	General population	O+ Group	O- Group	p*
Age (years)	47.1 ± 13. 7	47.5 ± 13.6	46.3 ± 13.2	0.42
Gender (N. %) **Men** **Women**	 193 (71.7%) 79 (28.3%)	 123 (70.3%) 52 (29.7%)	 70 (74.5%) 24 (25.5%)	0.26
Admission for (N. %) **Hematemesis** **Maelena** **Hematemesis and Maelena**	 85 (31.6%) 33 (12.3%) 151 (56.1%)	 60 (34.3%) 23 (13.1%) 92 (52.7%)	 25 (26.6%) 10 (10.7%) 59 (62.7%)	0.15

* test of Mann Whitney

Table 2: *Antecedents of patients*

Antecedents	O+ group (N, %)	O- group (N, %)	p**
Esophageal varices	34 (19.4%)	17 (18.1%)	0.11
Band ligation	00 (0.0%)	14 (14.9%)	0.002
Alcoholism	12 (6.8%)	17 (18.1%)	0.23
Alcoholism and tobacco smoking	08 (4.5%)	26 (27.7%)	0.08
Schistosomiasis	10 (5.7%)	06 (6.3%)	0.56
Cirrhosis	08 (4.5%)	05 (5.3%)	0.95
Hepatitis	03 (1.7%)	02 (2.1%)	0.78
Splenectomy	03 (1.7%)	02 (2.1%)	0.51

* $p < 0.05$ = significant comparison ; ** test of Mann Whitney

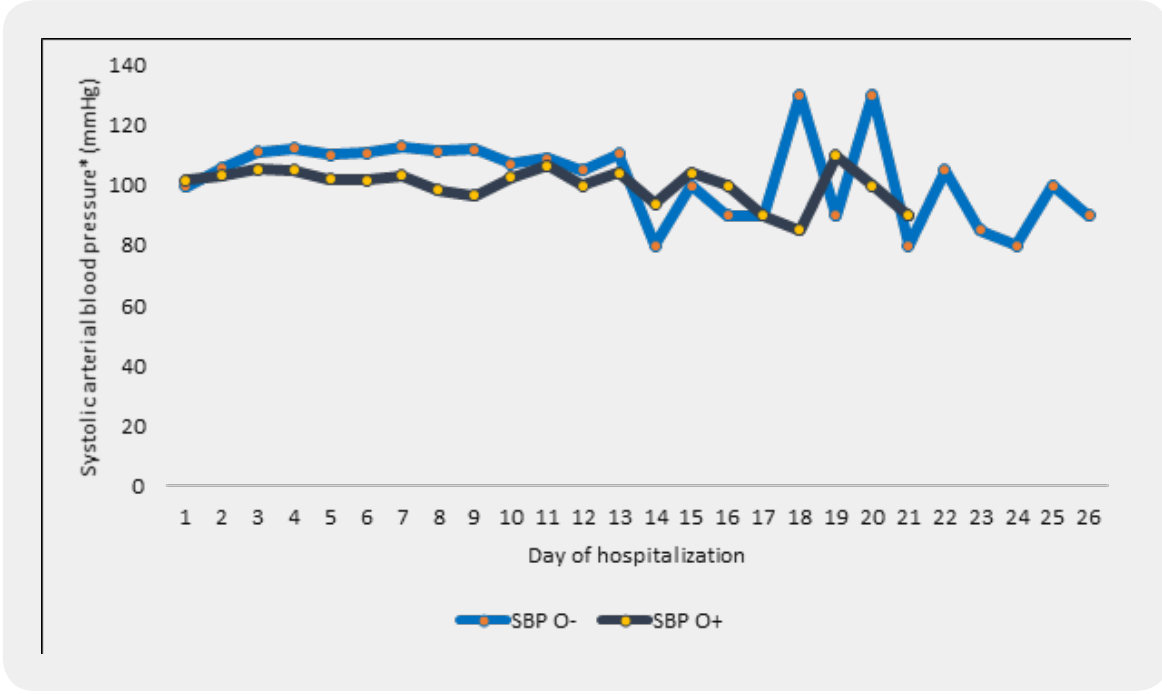
About the hemodynamic parameters of the whole population, systolic blood pressure (SBP) was 101.5 ± 10.9mmHg and mean arterial blood pressure (MAP) was 70.5 ± 6.8mmHg. The mean heart rate was 75 ± 11bpm with a shock index of 0.7 ± 0.2 (Table 3).

Table 3: *Hemodynamic in the general population*

Hemodynamic parameters**	Hemodynamic values	R	p***
SBP	101.5 ± 10.9	0.29	0.047
MAP	70.5 ± 6.8	0.33	0.023
HR	75.5 ± 11.3	0.05	0.73
Shock Index	0.7 ± 0.23	0.1	0.32

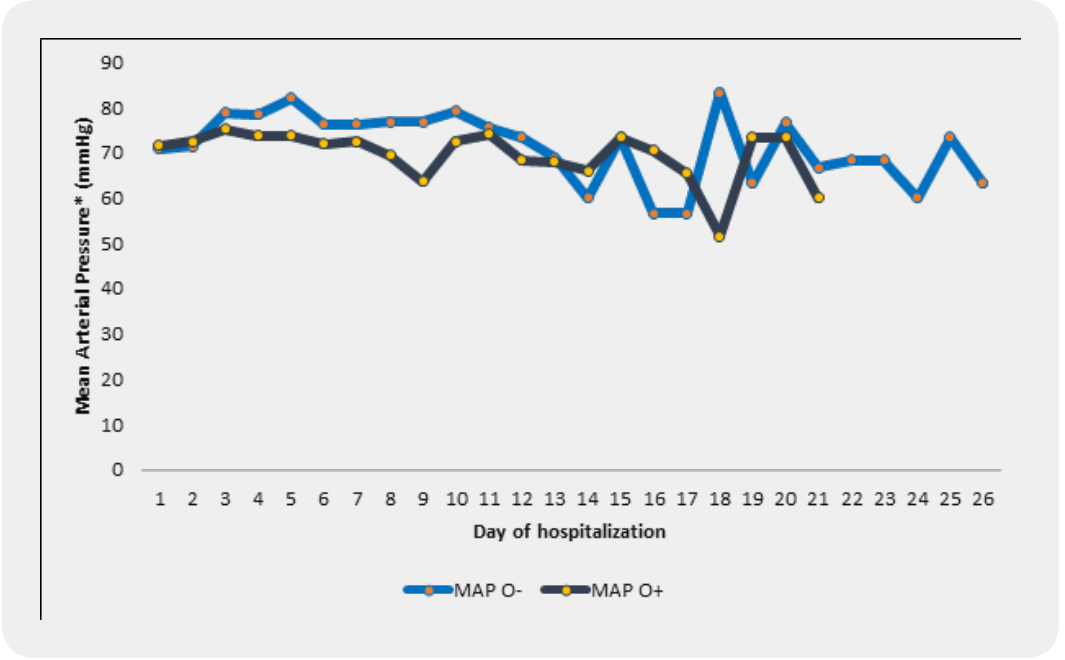
* $p < 0.05$ = significant correlation ; **in average ± standard deviation ; *** test of Pearson

Concerning hemodynamic parameters, both groups were comparable, particularly the systolic blood pressure (Figure 2) and heart rate (Figure 3). Nevertheless, the mean arterial pressure differed according to the use or not use of oxytocin ($p = 0.026$) (Figure 4).



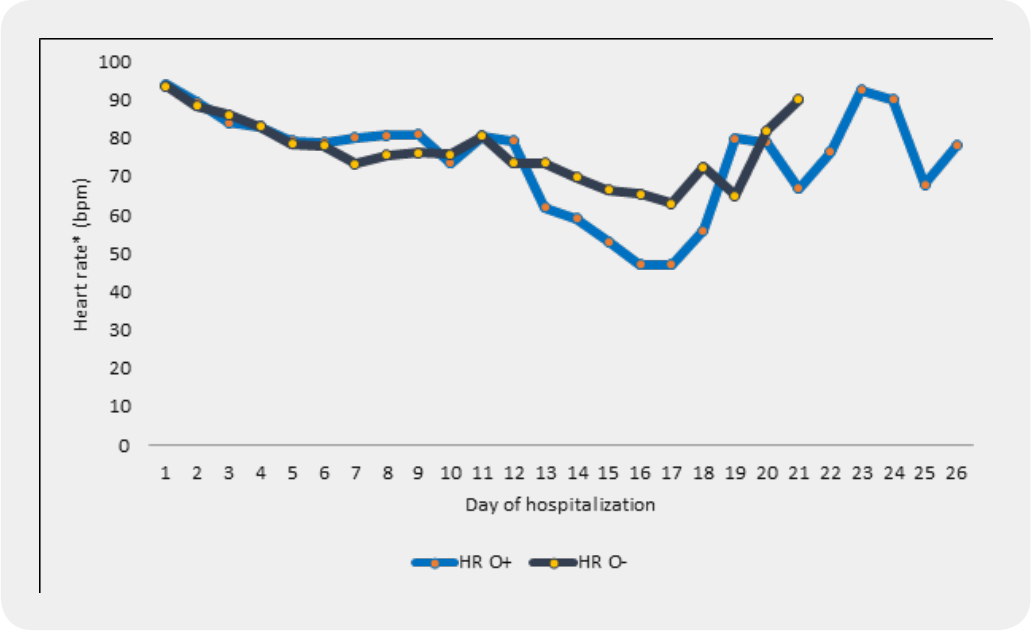
*SBP O- group = 100.3 ± 24.3mmHg. SBP O+ group = 98.5 ± 7.5mmHg ($p = 0.05$ (test of Mann Whitney)

Figure 2: *Comparison of systolic blood pressure between the two groups*



*MAP O- group = 72.4 ± 7.8mmHg. MAP O+ group = 69 ± 5.6mmHg (p = 0.026 (test of Mann Whitney)

Figure 3: *Comparison of mean blood pressure between the two groups*



*HR O- group = 77.5 ± 8.7 bpm. HR O+ group = 73 ± 13.7 bpm (p = 0.18 (test of Mann Whitney)

Figure 4: *Comparison of heart rate between the two groups*

The average hospital stay was 5.5 ± 3.4 days. Forty-three (43) patients died during hospitalization in intensive care, a mortality rate of 15.9%. The use of oxytocin had no impact on the survival and death of patients (p> 0.05) even if there was a difference in mortality between the two groups (18.3% vs 11.7%) (Table 4).

Table 4: *Outcome of the patients*

	O+ group	O- group	p*
Length of hospital stay (days)	5.1 ± 3.8	6.1 ± 4	**0.07**
Mortality (N, %)	32 (18.3%)	11 (11.7%)	**0.16**

* test of Mann Whitney

Discussion

This comparative retrospective study of variceal upper gastrointestinal bleeding and use of oxytocin demonstrated that the use of this drug had a significant impact on the average arterial blood pressure (especially mean arterial blood pressure) of the patients by decreasing it. In addition, its use had no impact on the morbidity and mortality of patients.

In the present study, VUGIB accounted for 1.4% of surgical intensive care unit admissions and 14.0% of all digestive hemorrhages. In a Tunisian study, gastrointestinal bleeding remains a common cause of hospitalization with a hospital prevalence of 5.3% [9]. In Europe, the varicose rupture is mainly related to chronic alcoholic liver disease which could explain the male predominance and especially affects the elderly over forty (also found in the present study = 47.1 years) [10,11].

In O+ group, oxytocin was used as soon as patients were admitted, with an average dose of 11.2 IU. Oxytocin (OT), a neuropeptide that is traditionally associated with female reproduction, has been implicated in several important cardiovascular functions including regulation of blood pressure [12]. Oxytocin may have played a role in stabilizing the hemodynamic status of patients. Its effects have been recently revised and several new roles on the cardiovascular system have been highlighted [13]. It has been identified as a cardiovascular hormone [14]. OT receptors have been found in the heart and blood vessels in humans. On the cardiovascular level, oxytocin activities include a decrease in blood pressure, a negative inotropic and chronotropic effect, neuromodulation of the parasympathetic system and vasodilation [13]. Thus, it could cause a decrease in portal pressure by decreasing vascular resistance.

The mortality rate for patients in this study during ICU was 15.9% and oxytocin had no impact on patient survival and death (p> 0.05). This mortality rate is quite low compared to the study of Razafimahefa H (26.5%) [15] and other African studies, such like reported by Bouglouga O [16], in Togo (25%) and Konate A [17] in Mali (50%). This is probably due to the lack of endoscopic or the no completion of the endoscopy within 12 hours after the bleeding accident and the lack of therapeutic resources such as the vasoactive drugs. Furthermore, in Madagascar, particularly, in Antananarivo, the band ligation is carried out, most often, far from the bleeding in the gastroenterology department of the Befelatanana University Hospital [18].

According to the consensus of BAVENO VI, it is essential to use the combination of a vasoactive drug and endoscopic treatment [19]. These vasoactive drugs reduce the splanchnic flow, which results in a decrease in variceal pressure [20,21]. These drugs are terlipressin [1-2mg every 4 hours (in the absence of coronary artery disease)] or somatostatin (250µg bolus then 250µg / h continuous intravenous) or somatostatin derivate (octreotide continuous intravenous 25µg /h) [22]. These latter should be started, if possible, before hospital admission [23]. Endoscopy should be performed as soon as possible in case of massive bleeding with hemodynamic repercussion and within 12 hours after admission in all cases. Per endoscopic hemostatic treatment of variceal rupture should be performed during the initial endoscopy. It is based on an elastic ligature in the case of esophageal varices and on sclerotherapy in case of rupture of gastric varices [19].

About the limits of the study, this drug (the oxytocin) was only used in the surgical intensive care unit of the CHU JRA in the treatment of variceal upper gastrointestinal bleeding; so, the results presented here do not reflect the management of VUGIB in other Malagasy hospitals. Also, this drug was off-label for the management of VUGIB. The study perspectives are to conduct a prospective study to verify our research hypothesis after having the marketing authorization of oxytocin.

Conclusions

The management of variceal upper gastrointestinal bleeding mainly relies on the optimization of mean arterial pressure. An observational and comparative study on the use of oxytocin in patients with VUGIB, in the surgical intensive care unit in a hospital of Antananarivo, has shown that this drug has cardiovascular properties, which could thus, act on mean arterial pressure without impact on mortality. Hemodynamic control plays an important role in the management of VUGIB; especially in Madagascar, where vasoactive drugs are not yet available. So, why not use other drugs that could reduce the hemodynamic parameters including the mean arterial blood pressure.

Conflicts of Interests

The authors have no conflict of interest.

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