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Recommended Citation

M. Soliman, Ashraf A.H and Elateif El Hakeem, Wael Abd (2022) "The role of sildenafil in perioperative management of patients with pulmonary hypertension undergoing lower limb vascular surgery," *Journal of Medicine in Scientific Research*: Vol. 5: Iss. 3, Article 11.
DOI: https://doi.org/10.4103/jmisr.jmisr_68_21

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The role of sildenafil in perioperative management of patients with pulmonary hypertension undergoing lower limb vascular surgery

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Abstract

Objective

To assess the role of sildenafil in perioperative management of patients with pulmonary hypertension undergoing lower limb vascular surgery.

Patients and methods

Twenty-four patients with pulmonary hypertension presented for lower limb vascular surgery were divided into equal groups, group 1 and group 2, each group having 12 patients.

Result

As regards demographic data, mean arterial pressure, and heart rate there were no statistically significant differences between both groups. As regards PaO₂ measured in arterial blood gases, pulmonary artery pressure, and ejection fraction, there was statistically significant differences between both groups.

Conclusion

We found that sildenafil has a unique effect in reducing pulmonary artery pressure, improving oxygenation, ejection fraction, and ICU stay.

Keywords: Lower limb vascular surgery, pulmonary hypertension, sildenafil

INTRODUCTION

When the WHO organized the first international conference on pulmonary hypertension (PH), there were no effective therapies, and median survival for patients with PH (now termed idiopathic pulmonary arterial hypertension) was under 3 years. Today, there are multiple therapies, and survival has more than doubled. As a result, more patients with PH undergo anesthesia and surgery. Successful management of the perioperative patient with PH requires multiple steps: recognizing the disorder, diagnosis the etiology, assessing severity of the disease, assessing the risk and benefit of anesthesia and surgery, developing an anesthesia plan, and managing the anticipated complication of systemic hypotension, and right-sided heart failure [1]. The pulmonary circulation I normally a low pressure [mean pulmonary artery pressure (PAP) 15 mmHg], low resistance circulation. PH is

defined as mean PAP more than 25 mmHg at rest [2]. The normal walled right ventricle decrease stroke volume in response to increase PAP and is unable to generate a mean PAP above 40 mmHg [3]. In patients with PH, altered vascular endothelial and smooth muscle function lead to vasoconstriction, localized thrombosis, and vascular growth and remodeling [4]. These processes increase pulmonary vascular resistance, resulting in right ventricle failure, inadequate oxygenation, and death. PH markedly increases morbidity and mortality among patients undergoing surgery. Understanding the pathophysiology of PH allows accurate risk assessment, optimization before surgery,

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Submitted: 21-Oct-2021 Revised: 12-Nov-2021 Accepted: 26-Nov-2021 Published: 23-Nov-2022

How to cite this article: M. Soliman AA, Elateif El Hakeem WA. The role of sildenafil in perioperative management of patients with pulmonary hypertension undergoing lower limb vascular surgery. J Med Sci Res 2022;5:266-9.

Access this article online

Quick Response Code:



Website:
www.jmsr.eg.net

DOI:
10.4103/jmsr.jmsr_68_21

and rational intraoperative and postoperative treatment [5]. Phosphodiesterase inhibitors has been demonstrated to treat PH by reducing cyclic guanosine monophosphate breakdown, making the pulmonary vascular smooth muscle more sensitive to endogenous and administered nitric oxide; this reduces the ventilation perfusion mismatch and hypoxia. Among the phosphodiesterase inhibitors studied, sildenafil has the greatest selectivity for the pulmonary circulation and arterial oxygenation [6]. Its proven effectiveness and safety in other forms of PH coupled with ease of oral administration means that it is a highly promising therapy for PH [7].

PATIENTS AND METHODOLOGY

Twenty-four patients presented to lower limb vascular surgery were enrolled in this study. Patients were randomly divided into two equal groups (12 patients each) by closed envelopes. Group 1: the control group.

Group 2: receive sildenafil 50 mg 1 h before anesthesia and then 50 mg twice daily postoperatively for at least 1 month.

Inclusion criteria

- (1) The patient selected according to American Society of Anesthesiologists (ASA) status (ASA 1 and ASA 2).
- (2) Normal coagulation profile.
- (3) Age range between 20 and 60 years.

Exclusion criteria

- (1) Renal or hepatic impairment.
- (2) Eisenmenger syndrome.
- (3) Systolic pulmonary blood pressure more than 70 mmHg.
- (4) Right ventricular failure.
- (5) Poor LVSF [ejection fraction (EF)<50%].
- (6) Concomitant use of drugs that interact with sildenafil, that is (nitrate or alpha blockers).

Preparation of the patient

All patients will be hospitalized for at least 1 week before anesthesia, after detailed history taking and through clinical assessment; laboratory assessment including CBC, PC, PT, INR, blood sugar, liver, and kidney function will be done. Also, ECG, echocardiogram, chest radiograph, and arterial blood gases will be done. Attempts to reduce PH before surgery will be performed on all patients, such as O₂ administrations, bronchodilators, and steroids. Patients receiving chronic therapy for PH will continue on such therapy. A dosage of 30 mg pethidine intramuscular was given as a premedication. Patients were fasting for 6–8 h before the procedure. Consent was taken from the patients for epidural anesthesia and the procedure was explained to the patients. Patients received sildenafil 50 mg 1 h before anesthesia.

Intraoperative

On arrival to the operating room, continuous monitoring with electrocardiography, pulse oximetry, and O₂ will be supplied 4 l/min through a face mask.

A suitable peripheral vein was cannulated with an 18 G cannula, under local anesthesia; radial artery and right

internal jugular vein will be cannulated. Baseline central venous pressure and arterial blood gases were monitored and before the start of anesthesia. Prehydration was achieved by infusing 500–1000 ml Ringer's solution for 1 h guided by 8–10 mmHg.

Anesthetic technique

Epidural anesthesia is given through the indwelling catheter inserted at L3–L4 interspace. Incremental doses (5 ml) of lidocaine (1%) and bupivacaine (0.25%) mixture (up to 20 ml) after a negative test dose (3 ml lidocaine 2% containing 5 µg/ml epinephrine) are given.

Monitoring

All patients were monitored by ECG, pulse oximetry; invasive blood pressure, CVP, and blood gases were also assessed (every hour).

Postoperative management

Patients will be transferred to the CCU and managed for 3 days. Group 2 will continue on sildenafil (50 mg twice daily); postoperative analgesia will be given by continuous infusion (0.06%) 8–12 ml/h. An epicardial transthoracic echocardiography will be performed postoperatively daily for 3 days and then after 1 month to provide information regarding pulmonary blood pressure and EF%.

Ethical considerations

The study was approved by the institutional Ethics Committee of National Heart Institute NO. HNI-00053.

Statistical analysis

All results were expressed as means (±SD), median (range), or number (%) of patients as appropriate. Repeated measures analysis of variance was used with post-hoc Dunnett's test for multiple comparisons against baseline value to further investigate any statistically significant findings. Ordinary data were analyzed using Mann–Whitney *U* test. Indices were analyzed using Fisher's exact test as appropriate. Statistical analysis was done using the computer program SPSS 16.0 for Microsoft Windows (SPSS Inc., Chicago, Illinois, USA). A *P* value less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the two groups as regards age, weight, height, and sex (Tables 1 and 2).

No significant differences in mean arterial pressure were found between the two groups before the administration of sildenafil and after administration of sildenafil (Table 3).

No significant differences in heart rate were found between the two groups before the administration of sildenafil. No significant changes in heart rate were observed after administration of sildenafil between the two groups (Table 4).

There is significant differences found between the two study groups regarding PaO₂ measured in arterial blood gases.

Table 1: Demographic data of study groups

	Control group (n=12)	Sildenafil group (n=12)
Age (years)	27.83±2.12	26.80±3.93
Weight (kg)	77.41±5.28	78.52±5.24
Height (cm)	166.91±2.46	165.88±3.49
BMI (kg/m ²)	33.09±0.81	32.06±1.31
Male sex	7 (58.3)	8 (66.6)

Data are represented as mean±SD and n (%).

Table 2: Intraoperative changes in mean arterial pressure

MAP (mmHg)	Control (n=12)	Sildenafil (n=12)
Baseline	81.75±8.63	80.16±8.34
At skin incision	82.00±8.62 [†]	78.50±7.75 [†]
End of surgery	80.91±6.03 [†]	79.16±5.71 [†]
Postoperative 5 min	79.25±8.63 [†]	78.50±7.75 [†]
Postoperative 30 min	83.08±7.45 [†]	82.82±7.43 [†]

Data are represented as mean±SD. MAP, mean arterial pressure.

[†]Significant difference versus baseline values within the same group.

Table 3: Intraoperative changes in heart rate

HR (min)	Control (n=12)	Sildenafil (n=12)
Baseline	85.66±8.87	86.08±6.15
At skin incision	79.00±8.780	79.83±5.82
End of surgery	79.66±8.52	80.25±5.81
Postoperative 5 min	81.50±8.82	81.91±5.86
Postoperative 30 min	77.83±8.74	80.166±5.89

Data are represented as mean±SD. HR, heart rate. [†]Significant difference versus baseline values within the same group.

Table 4: Partial pressure of oxygen in arterial blood gas measures recorded throughout the observation period

PaO ₂ (mmHg)	Control (n=12)	Sildenafil (n=12)
Baseline	56.16±5.06	58.66±4.29
At the end of surgery	58.33±5.245	74.58±4.03 ^{*†}
Postoperative (30 min)	59.00±4.95	93.33±3.49 ^{*†}

Data are represented as mean±SD. PaO₂, partial pressure of oxygen.

^{*}Significant difference between study groups (P<0.05). [†]Significant difference versus baseline values within the same group.

Table 5: Pulmonary artery pressures measures recorded throughout the observation period

PAP (mmHg)	Control (n=12)	Sildenafil (n=12)
Preoperative (baseline)	49.0 ±5.60	47.33±6.80
Postoperative (24 h)	48.41±5.68	43.00±6.66 ^{*†}
Postoperative (48 h)	48.91±5.29	40.58±6.52 ^{*†}
Postoperative (72 h)	49.50±5.72	38.41±6.90 ^{*†}
Postoperative (1 month)	51.91±5.915	34.50±4.92 ^{*†}

Data are represented as mean±SD. PAP, pulmonary artery pressure.

^{*}Significant difference between study groups (P<0.05). [†]Significant difference versus baseline values within the same group.

The sildenafil group recorded significant improvement in oxygenation in comparison with the other group (Table 5).

There are significant differences in PAP between the two groups. After the administration of sildenafil PAP decreased from 47 to 34 mmHg (P < 0.05) after 1 month. In the control group, no significant changes in PAP were observed (Table 6).

There are significant differences in EF between the two groups. After the administration of sildenafil EF increased from 56 to 62% (P < 0.05) after 1 month. In the control group, no significant changes in EF were observed (Table 7).

There are significant differences in ICU stay between the two groups. In the sildenafil group, there is short stay in the ICU (P < 0.05). All procedures were conducted without intraoperative and postoperative complications in the two groups.

DISCUSSION

In our study, we studied the effect of a perioperative oral dose of 50 mg of sildenafil 1 h before anesthesia and then 50 mg twice daily was given postoperatively for at least 1 month. The 12 patients undergoing lower limb vascular surgery with PH were compared with a control group of 12 patients, who did not receive sildenafil. In our study, there is no statistically significant difference between the two groups in mean arterial pressure. Also, there is no significant difference in heart rate between the two groups. There is improvement in arterial oxygenation tension (PaO₂ in ABG) in the sildenafil group, which increased from 58.66 mmHg (baseline) to 93.33 mmHg (postoperative 30 min). There is statistically significant decrease in pulmonary arterial pressure from 47 mmHg (baseline) to 34.50 (1 month postoperative). In the sildenafil group, there is statistically significant increase in EF from 56% (baseline) to 62.83% (1 month postoperative). There is significant improvement in the sildenafil group (short postoperative hospital stay). Similar to our study, Michelakis *et al.* [7], suggest that sildenafil may be superior to nitric oxide as sildenafil tended to decrease the pulmonary capillary wedge pressure.

Systemic arterial pressure did not decrease with treatment. The heart rate was not altered by treatment. The arterial oxygen saturation was improved by sildenafil; the preferential effect of sildenafil on pulmonary circulation probably reflects the high expression of this isoform in the lung.

Other studies also used different ways to assess the effect of sildenafil on PAP and hemodynamics. In study by Senzaki *et al.* [8] very recently it has been shown that the maximal hemodynamic effect of sildenafil on human circulation was achieved with a dose of 25 mg.

They also showed that maximal hemodynamic effects were achieved within 30 min after intake and the findings of this study were hand in hand with our study. Sildenafil might be a good candidate for long-term treatment of PH.

In Zhao *et al.* [9] study oral application of sildenafil showed a hemodynamic profile comparable to nitric oxide. Selective

Table 6: Ejection fraction% measures recorded throughout the observation period

EF%	Control (n=12)	Sildenafil (n=12)
Preoperative (baseline)	55.16±3.21	56.00±1.95
Postoperative (24 h)	54.50±2.81	58.83±1.58*†
Postoperative (48 h)	53.91±2.81	60.75±2.49*†
Postoperative (72 h)	53.83±3.18	62.33±3.14*†
Postoperative (1 month)	53.33±3.20	62.83±3.80*†

Data are represented as mean±SD. EF, ejection fraction. *Significant difference between study groups ($P<0.05$). †Significant difference versus baseline values within the same group.

Table 7: ICU stay

ICU stay (day)	Control (n=12)	Sildenafil (n=12)
	1.91±0.79	1.16±0.38*†

Data are represented as mean±SD. *Significant difference between study groups ($P<0.05$). †Significant difference versus baseline values within the same group.

pulmonary vasodilatation without significant systemic hypotension was also achieved with systemic application of sildenafil. The effect of selective vasodilation may be due to different distributions of phosphodiesterase-5 in different vascular beds phosphodiesterase-5 is expressed in relatively high amounts in the lung vasculature and the corpus cavernosum [10]. A high level of phosphodiesterase-5 expression in pulmonary arteries provides a good explanation for the pulmonary selective vasodilatation property of sildenafil as observed. In patients with severe PH, a dose of 50 mg of sildenafil (like doses in our study caused substantial effects on pulmonary circulation without significant systemic side effect in patients with PH). In our study anesthesia is an excellent choice in patients with PH. Also Smedstad *et al.* [11] reported that cases with primary PH were successfully managed with epidural anesthesia and showed that sildenafil as a new investigational drug is used in combination with inhaled NO decreases PAP. It has the advantage of oral medication and can take regularly.

CONCLUSION

We conclude in our study that sildenafil has a unique effect in reducing PAP, improving oxygenation, EF%, and patient outcome (improve dyspnea, fatigue, and a decrease in intensive care stay) without systemic hypotension.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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