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Original Research / Özgün Araştırma

Changes in blood pressure, blood sugar and creatinine in patients undergoing pheochromocytoma surgery

Feokromositoma ameliyatı geçiren hastalarda kan basıncı, kan şekeri ve kreatinin değişiklikleri

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Özet

Amaç: Kan basıncı ve kan şekeri seviyelerindeki değişiklikleri tahmin edebilecek değişkenleri keşfetmek ve feokromositomalı hastalarda bu tür değişikliklerin meydana geldiği zaman dilimini kesin olarak belirlemek.

Gereç ve Yöntemler: 20 aylık bir süre boyunca feokromositoma nedeniyle ameliyat edilen ardışık hastalar bu etik inceleme kurulu onaylı, prospektif kohort çalışmasına dahil edildi. Kan basıncı ve şeker seviyeleri, perioperatif dönemde ve ardından ameliyattan 3 ay sonra sabit bir protokol kullanılarak seri olarak izlendi. Değişiklikler karşılaştırıldı ve öngörücü faktörler için değerlendirildi.

Bulgular: Çalışmaya cerrahi girişim uygulanan 50 hasta dahil edildi ve bunların %32'sinde ameliyattan sonra hipotansiyon ve %10'unda hipoglisemi gelişti. Tüm hipotansiyon atakları ameliyattan sonraki 6 saat içinde meydana geldi. Ancak hipoglisemi gelişen 8 hastadan 7'si ameliyattan sonraki ilk 4 saat içinde ortaya çıkarken, biri 12 saat sonra ortaya çıktı. Hipotansiyon oluşumu, ameliyat öncesi 24 saatlik idrar vanililmandelik asit seviyeleri ile koreledir (p=0,024). 21 hipertansif hastadan 15'inde 3. ayda kalıcı hipertansiyon vardı ve bu yaş (p=0,04) ve başvuru anındaki diabetes mellitus (DM) ile ilişkiliydi.

Sonuç: Feokromositoma cerrahisi alan hastaların %32'si inotropik desteğe ihtiyaç duyan postoperatif hipotansiyon yaşadı. Daha yüksek dozlarda alfa-blokörlere ihtiyaç duyan veya 24 saatlik idrar VMA seviyeleri daha yüksek olan hastalar bunu yaşamaya daha

Abstract

Objective: To discover the variables that may predict changes in blood pressure and blood sugar levels and to pinpoint the time frame during which such changes occur in patient with pheochromocytoma.

Material and Methods: Consecutive patients undergoing surgery for pheochromocytoma over a 20-month period were included in this ethics review board-approved, prospective cohort study. Blood pressure and sugar levels were serially monitored using a fixed protocol in the perioperative period and subsequently at 3 months after surgery. Changes were compared and assessed for the predictive factors.

Results: Fifty patients undergoing surgical procedures were included in the study of whom 32% developed hypotension and 10% developed hypoglycaemias after surgery. All hypotension episodes occurred within 6 hours of surgery. However, while 7 of 8 patients who developed hypoglycaemia manifest in the first 4 h after surgery, one occurred after 12 h. Occurrence of hypotension correlated with preoperative 24-h urinary vanillylmandelic acid levels (p=0.024). Out of 21 hypertensive patients, 15 had persistent hypertension at 3 months and this was associated with age (p=0.04) and diabetes mellitus (DM) at presentation.

Conclusion: 32% of patients receiving pheochromocytoma surgery experienced postoperative hypotension needing inotropic support. Patients who require greater dosages of alpha-blockers or those with higher 24-h urine VMA levels are more prone to experience

The study was approved by Ethics Committee of SMS Medical College (Approval Date: 2022-03-19 and Approval Number: 911-MC-EC-2021). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

yatkındır. Bu, ameliyattan sonraki ilk altı saat içinde gerçekleşir. Daha yaşlı veya uzun süredir DM'si olan hastaların ameliyattan sonra kronik HTN'den muzdarip olma olasılığı daha yüksektir.

Anahtar Kelimeler: Feokromositoma, hipertansiyon, hipoglisemi, kreatinin

this. This happens within the first six hours following surgery. Patients who are older or who have had DM for a long time are more likely to suffer chronic HTN following surgery.

Keywords: Pheochromocytoma, hypertension, hypoglycaemia, creatinine.

INTRODUCTION

Pheochromocytoma (PC) are tumours that develop from chromaffin cells of the adrenal medulla. They can make, process and release catecholamines. Because of their influence on hemodynamic and metabolism, catecholamines produced by tumours are too responsible for a wide range of manifestations and symptoms (1, 2). Secondary hypertension (HTN) is commonly brought on by neuroendocrine tumours, which emit too much catecholamine (3). The main form of treatment is surgical extirpation, with minimally invasive surgery being the accepted method (4,5). These individuals are vulnerable to developing postoperative hypotension after the source of excessive catecholamines is eliminated, hence careful preoperative and intraoperative control is necessary to prevent hemodynamic instability (1). Moreover, PCs are suspected to trigger diabetic mellitus (DM) because to increased gluconeogenesis and glycogenolysis resulting from an excess of catecholamines, and following tumour removal, these patients may have serious hypoglycaemia, which can be lethal if not treated. (6, 7). Thus, it is crucial to keep an eye out for hypotension and hypoglycaemia in these individuals throughout the early postoperative period. The length and frequency of this monitoring have not been determined, though. In addition, following surgery, up to 90% of diabetes individuals risk becoming euglycemic and up to 50% of patients with hypertension may fully cure the condition over time, coupled with changes in body mass index (BMI) that may influence their quality of life (QoL) (8–10). Since muscle is the main source of creatinine, catabolic states are caused by an excess of catecholamines, and their reversal following surgery is shown by a rise in blood creatinine levels.

The purpose of this prospective cohort study is to identify the factors which may predict alterations in blood pressure and blood glucose level, as well as the timelines in which such changes occur. This might aid in identifying which individuals require more comprehensive and sustained monitoring. Furthermore, we examined the prevalence of chronic DM and HTN along with changes in BMI and serum creatinine.

MATERIAL AND METHODS

The SMS Medical College and Hospital's Institutional Ethics Committee accepted this prospective study, which was conducted from June 2021 to June 2022. The criteria of the International Conference on Harmonization's Good Clinical Practice (ICH-GCP) were observed for carrying out the present research. Written consent in vernacular language has been obtained from each participant before enrolling in to the study.

Inclusion Criteria

Adult patients (age 18 years or older) diagnosed with pheochromocytoma, patients scheduled to undergo surgical resection of pheochromocytoma, patients who are willing to participate in the study and provide informed consent, patients who are able to attend follow-up visits as per study protocol, patients with no history of previous pheochromocytoma surgery, patients with no known history of other medical conditions that may impact blood pressure or blood sugar levels, such as renal failure. Exclusion criteria were : Age less than 18 years were excluded, nonsurgical candidates of pheochromocytoma were excluded, patients with other metastatic disease were excluded, patients with a history of previous pheochromocytoma surgery, patients with known

history of other medical conditions that may impact blood pressure or blood sugar levels, such as renal failure, patients who are unable to provide informed consent or attend follow-up visits as per study protocol, patients who are pregnant or breastfeeding.

Pheochromocytoma was diagnosed using standard criteria for biochemical and radiological examination. Patients with metastatic disease and non-surgical candidates were excluded. Alpha-antagonists were used as the initial medicine in conjunction with antihypertensive drugs to reduce increased blood pressures prior to surgery. Prazosin was the primary alpha-blocker employed, with calcium channel blockers supplemented when the pressure control was insufficient. In order to manage the tachycardia brought on by alpha blockage, beta-antagonists were added. The preparation's ultimate objectives were a haematocrit below 40%, a healthy blood pressure, and minimum or even absence of orthostatic hypotension. To facilitate volume expansion, patients were advised to consume up to 5 g of salt per day and roughly 4-5 litters of water daily.

In an excel sheet, data were prospectively recorded. Demographic information, clinical and tumor features, BMI, serum creatinine and 24-hour urine catecholamine levels were all preoperative factors. Antihypertensive and hypoglycaemic medications with the appropriate dosages, baseline blood pressure and glucose levels, and other data were also collected.

The kind of surgery (laparoscopic or open), the length of the procedure, problems during the hospital stay, blood loss, and blood transfusions were all considered operational criteria. Intraoperative volume monitoring was performed using central venous pressure as well as a catheter placed across the right jugular vein. For the treatment of HTN and hypotension, there were established regimens. Sodium nitroprusside (SNP) was infused intravenously at a dosage of 0.5 to 5 g/kg/min to manage intraoperative hypertension. Boluses of esmolol (10–20 mg) were administered as necessary to manage tachycardia. Following tumour separation, crystalloids were first used to resuscitate the patient's volume. Colloids (hydroxyethyl starch) were administered if the hypotension, which is characterised by a systolic blood pressure less than 90 mmHg, did not improve after receiving a crystalloid stream. Noradrenaline (given as an infusion at a rate of 2–20 mcg/min) was initially selected as a vasopressor for the treatment of hypotension following volume resuscitation. Hypotension that did not respond to conventional vasopressors was treated with vasopressin, dopamine, and adrenaline.

Immediately following surgery, blood sugar levels were checked in interval of 2 hours for minimum 12 hours, and then every 4 hours after that. Until patients could begin oral intake, 2 ml/kg/h of postoperative intravenous fluids were administered. Ringer's lactate or acetate were the options for intravenous fluids; however, 5% dextrose normal saline was substituted if blood glucose levels ever fell below 120 mg/dL. Blood glucose levels of less than 80 mg/dL were considered hypoglycaemia and a 25% glucose bolus was used to treat it.

During the patient's stay in the intensive care unit (ICU) and after being shifted to the wards, postoperative blood pressure and blood sugar levels were checked until the patient was discharged. The database contained information on the dosage, duration, and need for dextrose bolus. Following surgery, the patients underwent reviews two weeks, six weeks and three months later with blood pressure and blood sugar readings taken at each session. At three months, BMI and serum creatinine were measured. Patients were classified as having persistent HTN or DM, respectively, if they still needed antihypertensive or hypoglycaemic therapy after three months.

Statistical Analysis

At the conclusion of the trial, the data were input into an excel spreadsheet and examined using the programme to look for preoperative and intraoperative factors that could have affected outcome metrics. GraphPad 3.0 was used to analyse the data, and the results were displayed as mean standard deviation or median (range). Frequency was used to depict categorical values (percentage).

Univariate and multivariate Cox proportional hazard regression models were used to investigate the associations between dependent and independent variables. Continuous variables were analysed using the Wilcoxon rank sum test, and categorical variables were compared using the Chi-square test. The paired t-test was used to evaluate within-group variations in scores. To determine the connection between two continuous variables, Spearman correlation coefficient was utilized. Statistics were deemed significant at $p<0.05$.

RESULTS

Total 50 patients, comprising 25 men and 25 women, met the inclusion criteria during the research period. Their average age was 40.6 ± 14.3 years, and the average number of months they had symptoms was 28.2 ± 6.5 months. Of these 50 individuals, 7 had inherited disorders, including 2 cases of von Hippel-Lindau disease and 5 cases of the multiple endocrine neoplasia-2 (MEN-2) syndrome, whereas the remaining 43 cases of PC were sporadic. Six patients got open surgery, whereas forty-four patients underwent laparoscopic surgery. In open surgery, larger masses were operated and the operation time was longer as compared to laparoscopic surgery. In Tables 1 and 2, respectively, the demographic and surgical parameters are shown.

Table 1. Baseline characteristics of patients

Age years	40.6 ± 14.3
BMI kg/m2	26.8 ± 5.2
Gender: Male/Female	25/25
Sporadic PC n (%)	43 (86%)
Hereditary syndromes n (%)	7 (14%)
MEN – 2 syndromes n (%)	5 (10%)
von Hippel–Lindau Disease n (%)	2 (4%)
Mean duration of symptoms Months	28.2 ± 6.5

Data were expressed as Mean ± SD. **BMI;** Body Mass Index, **PC;** Pheochromocytoma, **MEN – 2 syndromes;** Multiple Endocrine Neoplasia – 2 syndromes.

Inotropic assistance was needed in 16 patients (or 32%) in the postoperative term. None of these patients experienced delayed onset hypotension; all of them experienced it immediately after surgery. The first inotrope was a noradrenaline infusion. One patient needed an infusion of noradrenaline and adrenaline, and another needed an infusion of dopamine. The average time for infusion of noradrenaline was 16.6 hours, and the average dosage needed was 7.4 g/min. Preoperative 24-hour urine vanillylmandelic acid (VMA) levels and the incidence of hypotension were both linked (p=0.04). Urinary VMA and daily prazosin dosage were correlated with a 0.5 Spearman correlation value that was statistically significant (p=0.04). These relationships are shown in Table 3.

Table 2. Surgical Outcomes of patients

Parameter	Total	Open Surgery	Laparoscopic Surgery
Patients, n	50	6	44
Procedures, n	60	6	54
PC/PG, n	42/8	2/4	40/4
Tumor Size (cm)	5.06 ± 1.89	6.10 ± 2.10	4.02 ± 1.68
Operative time (min)	168.71 ± 64.51	198.14 ± 81.38	139.28 ± 47.64

Data were expressed as Mean ± SD. **PC;** Pheochromocytoma, **PG;** paragangliomas

Table 3. Variables predicting hypotension

Parameters	Inotropic required No (n=34) (%)	Inotropic required Yes (n=16) (%)	p value
Age (years)	38.49 ± 9.18	42.71 ± 9.42	0.81

Gender n (%)			0.99
Male	13 (52%)	12 (48%)	
Female	13 (52%)	12 (48%)	
Hypertension on presentation			0.99
Yes	31	16	
No	3	0	
Diabetes on presentation			0.37
Yes	8	5	
No	26	11	
Hereditary syndrome (MEN2/VHL), n (%)			<0.05
Yes	7 (100%)	0	
No	27 (62.79%)	16 (37.21%)	
S. Creatinine	0.5 ± 0.08	0.59 ± 0.09	0.02
Duration of symptoms months	12	12	0.99
Tumor size cm	5.22 ± 1.99	4.9 ± 1.79	0.68
24-hour urinary VMA (mg/24 hour)	18.60 ± 6.3	33.68 ± 9.2	0.024
Number of antihypertensive	2	2.5	0.14
Daily dose of prazosin (mg)	3	12.5	0.04

Data were expressed as Mean ± SD. **BMI;** Body mass index, **VHL;** Von Hippel-Lindau, **MEN2;** Multiple endocrine neoplasia 2, **VMA;** Vanillylmandelic acid, **HTN;** Hypertension

Table 4. Variables predicting persistent hypertension

Parameters	Hypertension at 3 months No (n=35)	Hypertension at 3 months Yes (n=15)	p value
Age (years)	34.59 ± 9.25	46.61 ± 9.35	0.03
Gender n (%)			0.98
Male	17 (48.57%)	8 (53.33%)	
Female	18 (51.43%)	7 (46.67%)	
Hypertension on presentation			0.96
Yes	32	15	
No	3	0	
Diabetes on presentation			0.04
Yes	4	9	
No	31	6	
Hereditary syndrome (MEN2/VHL), n (%)			0.63
Yes	6	1	
No	29	14	
S. Creatinine	0.69 ± 0.07	0.76 ± 0.13	0.03
Duration of symptoms months	18	24	0.41
Tumor size cm	5.3 ± 1.99	4.8 ± 1.79	0.21
24-hour urinary VMA (mg/24 hour)	20.30 ± 6.8	29.56 ± 8.4	0.70
Number of antihypertensive	2	3	0.26
Daily dose of prazosin (mg)	4	4	0.99

Data were expressed as Mean ± SD. BMI; Body mass index, VHL; Von Hippel-Lindau, MEN2; Multiple endocrine neoplasia 2, VMA; Vanillylmandelic acid, HTN; Hypertension

Following excision of the tumour, hypoglycaemias occurred in five individuals, necessitating dextrose infusion. At the presentation, just one of them had diabetes. One of these patients had hypoglycaemias after 12 hours, whereas the other four patients experienced it within the first four hours following surgery. These patients required dextrose infusion for a mean of 24 hours, and once dextrose infusion was terminated, none of these patients experienced any subsequent hypoglycaemias. Univariate analysis revealed no association between the requirement for a dextrose infusion and any preoperative catecholamine levels, clinical history, or tumour features.

At the time of presentation, 47 patients had hypertension, and 15 (31.91%) of these still had it after three months, necessitating the use of antihypertensive medications. None of the previously normotensive individuals experienced new-onset HTN, and all of these patients had hypertension upon discharge. One patient continued to require the same dosages of antihypertensives, while thirteen of the fifteen patients needed less antihypertensives overall. Age and diabetes mellitus at presentation showed a significant correlation in univariate analysis ($p=0.03$ and 0.04, respectively), and older patients or those with diabetes mellitus had a higher risk of continuing HTN (Table 4). Only one of the thirteen patients who had diabetes at the time of presentation still had it three months following surgery. For almost 4 years, this patient's diabetes had been well-known. No correlation analysis could be done since there was just one patient with chronic DM. Following surgery, there was a substantial rise in the mean BMI and serum creatinine, with increases in the mean BMI of 1.93kg/m^2 ($P<0.001$) and 0.12 mg/dl ($P<0.05$), respectively.

DISCUSSION

Patients who have surgical excision of a pheochromocytoma run the risk of developing severe hypotension as a result of the sudden removal of catecholamines from the bloodstream while still receiving ongoing alpha-blockade. This needs cautious monitoring since it might cause ischemic end-organ damage. Patients frequently require inotropic assistance to keep their blood pressure stable (1). In our research, 32% of the patients required inotropic assistance. We discovered a correlation between the total daily dose of alpha-blockers and the requirement for inotropic assistance. This might be the result of ongoing alpha-blockade following excision of the tumour, which results in unopposed vasodilation. Our results support a previous study that found postoperative hypotension occurs more frequently in patients with fewer intraoperative pressure increases (11). This effect is more pronounced following use of the long-acting alpha-blockers doxazosin and phenoxybenzamine. This effect may be caused by stronger and longer acting alpha-blockers. This is in line with recent studies examining the impact of alpha-blockers on postoperative hypotension, which show that patients on alpha-blockers experience postoperative hypotension more frequently than those taking calcium channel blockers (12,13). Namekawa et al. similarly reported that patients receiving higher doses of prazosin exhibited significant postoperative hypotension (14), which is consistent with our findings.

According to Shao et al., alpha-blockers had little effect for preserving intraoperative hemodynamic stability in patients with normotensive PC (15). Instead, they increase the necessity for colloid infusion and the use of vasoactive drugs. Although it raises the possibility of intraoperative severe HTN, this may help reduce such hypotension episodes.

Inotrope requirements were related to preoperative 24-hour urinary VMA levels. For blood pressure management, the individuals with higher VMA levels needed larger daily dosages of prazosin. This shows that more hormonal activity raises the risk of surgical hypotension and necessitates more preoperative alpha-blockade. According to some writers, there is a strong correlation between preoperative catecholamine levels and postoperative hemodynamic instability (14).

Additionally, the patients who had normotension at the time of presentation maintained it throughout the recovery period. This information is crucial for creating a plan for their postoperative care. For these

patients, a typical 24-hour stay in the ICU may be reduced to 6-8 hours. Bénay et al. have also made recommendations along the same lines (12).

Although five individuals required dextrose infusion due to hypoglycaemia, there were no risk factors and non-diabetic patients were equally vulnerable. Even in patients who initially stay normoglycemic in the postoperative phase, blood glucose level screening should be kept for up to 24-48 h since one patient developed hypoglycaemia after 12 h. According to Plouin et al., no correlation was found between surgical hypoglycaemia (15.15% of patients) and preoperative hyperglycaemia or plasma catecholamine concentrations (16). On the other hand, Chen et al. showed a relationship between bigger tumours and serum 24-hour urine metanephrine as well as longer operating times. (7) This consequence occurred between 0.4- and 142-hours following surgery, emphasising the need for continued blood sugar monitoring even after the patient was moved out of the intensive care unit (7).

Surgery for pheochromocytoma causes major metabolic alterations, including the remission of HTN, diabetes, and a more favourable body fat distribution, which raises BMI and serum creatinine (8,9,10). Pogorzelski et al. claim that the period between discharge and three months following surgery is when HTN and diabetes are improved the most, and that this period is followed by a year of benefits (10). After pheochromocytoma surgery, the frequency of chronic HTN ranges from 7% to 58% (8,17,18). We discovered that the patient's age (p=0.04) and diabetes (p=0.04) upon presentation were the only variables significantly linked with persistent HTN. In a long-term follow-up research after pheochromocytoma surgery, Poulin et al. discovered that age and family history of HTN were the only characteristics linked with persistent hypertension in 30.6% of patients at 1 year(16). They suggested that after removing the PC, there may still be an important HTN component that increases with age. In a different research, Sapienza et al. discovered that age was the only predictor that was substantially linked with chronic HTN, which affected 29% of patients (2).

The correlation between persistent HTN and DM at presentation may be caused by microvascular alterations brought on by chronic DM. In patients with chronic HTN, the median duration of diabetes at presentation was 48 months (ranging from 12 to 60), in contrast to 6 months in individuals who did not have ongoing high blood pressure. We were unable to locate another trial in which DM was linked to long-lasting HTN.

According to Pogorzelski et al., during the one-year follow-up, up to 90% of patients had euglycemia whereas 70% of patients promptly stopped taking hypoglycaemic medications after surgery (9). Spyroglou et al. recently showed that compared to 21% preoperatively, after a year, 9.3% of PC patients had diabetes. (comparable to the general population) (12). Only one patient had diabetes following surgery, indicating a sizable potential benefit.

Another significant symptom of pheochromocytoma is hypermetabolic state induced by the catecholamine, which causes weight loss even though normal appetite and food intake (6,2). Petrák et al. found that a small sample of 17 patients who had adrenalectomy for pheochromocytoma saw a considerable improvement in BMI and a good distribution of body fat (20). In their retrospective analysis including 43 PC patients, Spyroglue et al. similarly noted a substantial rise in BMI at 1 year (10). In prospective research, Bosanka et al. found that 18 PC patients' BMI significantly increased six months following surgery (21). After 3 months following surgery, we discovered a mean rise in BMI and serum creatinine of 1.93kg/m^2 ($P < 0.0001$) and 0.12mg/dl ($P<0.05$) respectively. The postoperative increase in creatinine in the entire group of patients demonstrates the catabolic condition generated by catecholamine excess and its reversibility after surgery. This might be due to muscle wasting, as muscular tissue is the major source of the circulating pool of creatinine, for example, and muscle loss has recently been documented in individuals with Pheochromocytoma. (22)

Limitation of the Study

Small sample size: Depending on the number of eligible patients, it may be difficult to recruit a large enough sample size to detect real statistically significant differences in outcomes.

Non-randomized design: Because this is a prospective cohort study, patients are not randomly assigned to treatment groups, which could introduce bias and affect the internal validity of the study.

Lack of blinding: Because this study involves surgical intervention, it may not be possible to blind participants or researchers to treatment group, which could also affect the internal validity of the study.

Follow-up period: The study may have a limited follow-up period, which could make it difficult to assess long-term outcomes or potential complications that may arise over time.

Single-centre study: The study may be limited to a single centre, which could limit the generalizability of the findings to other settings or populations.

Strength

Prospective Design: This study is prospective, which means that it will follow patients over time and collect data as events occur, which can provide more robust data than retrospective studies.

Cohort Design: The cohort design allows for comparison between patients who receive the surgical intervention, which can provide valuable information about the effectiveness of the intervention.

Multidimensional Outcomes: The study is evaluating multiple outcomes of interest, including blood pressure, blood sugar, predictors for their changes, which can provide a more comprehensive understanding of the impact of the surgical intervention on patients.

Consistent Protocol: The study will follow a consistent protocol for surgical intervention and data collection, which can reduce the potential for bias or error in the study results.

Clinical Relevance: Pheochromocytoma is a rare and potentially life-threatening condition, and the study has the potential to provide valuable information about predictors for the blood pressure, blood sugar changes, the effectiveness of surgical intervention on outcomes of interest to patients and clinicians.

CONCLUSION

In conclusion, this study highlights several potential complications that may occur following pheochromocytoma surgery. This complication was observed within the first six hours after surgery and mostly occurs in patients having higher 24-h urine VMA levels or who required higher doses of alpha-blockers. Additionally, postoperative hypoglycaemias were seen in a minority of patients, with a higher risk in those who were older or had a longer history of diabetes mellitus. These findings suggest that careful monitoring and management of blood pressure, blood sugar, and other relevant parameters in first six hours may be crucial and necessary for patients undergoing pheochromocytoma surgery, particularly in those with higher risk factors for complications. By considering these we may avoid the life-threatening complications.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ethics Committee of SMS Medical College (Approval Date: 2022-03-19 and Approval Number: 911-MC-EC-2021). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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