



Pregnancy-Related Hypertension in Multigravidas with Previous Cesarean Delivery

Geçirilmiş Sezaryenle Doğum Öyküsü Olan Multigravidalarda Gebeliğe Bağlı Hipertansiyon

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Objective: To investigate whether prior cesarean delivery is associated with occurrence of pregnancy hypertension.

Methods: A prospective case-control study in consenting eligible consecutive 475 pregnancies with prior cesarean delivery and age- and parity-matched 475 pregnancies with previous vaginal delivery. Results were subjected to multiple logistical regression analysis.

Results: Body mass index, birth interval, and neonatal birth weight were comparable between the study groups. In women with prior cesarean delivery, pregnancy-related hypertension was significantly higher [15.9% vs. 6.7% in those with prior vaginal delivery, $p < 0.05$; odds ratio (OR), 2.6; 95% confidence interval (CI), 1.707–4.072]. A higher proportion of women were found to develop hypertension by 32 weeks of pregnancy. In both the study groups, the development of pregnancy-related hypertension was found to be higher in the age group of 20–25 years, birth interval of > 18 months, second gravidas, and in the gestation period between 32 and 36 weeks. Number of women with severe disease was higher in both the groups.

Conclusion: Pregnancy-related hypertension is more common in women with prior cesarean delivery, and it occurs at earlier gestation weeks than in those without prior cesarean delivery. In multigravidas, severe forms of the disease are more common.

Keywords: Multigravida, pregnancy hypertension, previous cesarean delivery

Amaç: Çalışmanın amacı geçirilmiş sezaryen ile gebeliğe bağlı hipertansiyon arasında bir ilişki olup olmadığını araştırmaktır.

Yöntemler: Bu prospektif vaka kontrollü çalışma, geçirilmiş sezaryen doğumu olan 475 gebe ile geçirilmiş vajinal doğum öyküsü olan ve yaş ve parite açısından eşleştirilmiş 475 gebelerle yapılmıştır. Sonuçlar çoklu lojistik regresyon analizi ile değerlendirilmiştir.

Bulgular: Vücut kitle indeksi, doğum aralığı ve neonatal doğum ağırlığı çalışma grupları arasında benzerdi. Geçirilmiş sezaryen doğumu olan kadınlarda gebeliğe bağlı hipertansiyon, geçirilmiş vajinal doğumu olanlara göre anlamlı derecede daha yüksek bulundu [sırasıyla, %15,9 ve %6,7, $p < 0,05$; odds ratio (OR), 2,6; %95 güven aralığı (CI), 1,707–4,072]. Kadınların büyük bir oranında gebeliğin 32. haftasında hipertansiyon gelişmiş olduğu görüldü. Her iki çalışma grubunda da gebelik ile ilişkili hipertansiyon gelişimi, 20-25 yaş aralığında, 18 aydan fazla doğum aralığı olanlarda, ikinci gravidalarda ve 32. ile 36. gebelik haftaları arasında kalan periyotta daha yüksek olarak bulundu. Ağır hastalığı olan kadınların sayısı her iki grupta da yüksekti.

Sonuç: Gebeliğe bağlı hipertansiyon geçirilmiş sezaryen öyküsü olan kadınlarda, olmayanlara göre daha sıktır ve gebeliğin erken döneminde ortaya çıkar. Multigravidalarda hastalığın ağır seyri daha yaygındır.

Anahtar kelimeler: Multigravida, gebeliğe bağlı hipertansiyon, geçirilmiş sezaryen

Introduction

Pregnancy-related hypertension is a significant contributor to maternal as well as perinatal morbidity and mortality and is found to be responsible for 25% of maternal mortality (1). There are several factors that can place a woman at a higher risk of developing pregnancy hypertension. Potential risk factors associated with the development of hypertension in pregnancy include multiple gestation, nulliparity, pre-existing diabetes, high body mass index (BMI), advanced maternal age, and history of hypertension in previous pregnancies (2).

Pregnancy-related hypertension is generally considered as a disease of first pregnancy. It is less common in subsequent pregnancies. If a woman was normotensive during her first pregnancy, the possibility of developing hypertension in a subsequent pregnancy was much lower (3). There are studies documenting the risk of recurrence (4, 5) and occurrence of pregnancy hypertension in multigravidas (6).

Not many studies have been performed to determine the changing incidence of pregnancy-related hypertension in multigravidas. It is acknowledged that the incidence of cesarean delivery has been on the rise. It is also documented that a scarred uterus can affect the vasculature of the uterus and may subsequently affect the placentation in pregnancy (7). It is also established that the primary pathology of preeclampsia appears to be at the maternal–fetal interface characterized by poor trophoblastic invasion of the uterus and that it subsequently alters the utero-placental blood flow (8). It is reported that there is an increased preeclampsia risk in the following pregnancies after cesarean delivery (9).

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Received/Geliş Tarihi: 02.01.2017

Accepted/Kabul Tarihi: 25.03.2017

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The present study is an attempt to recheck the influence of prior cesarean delivery on incidence of pregnancy-related hypertension.

Methods

This was a prospective case-control non-interventional study conducted from September 2015 to August 2016 in maternity facilities attached to a medical college in southern India on the west coast.

Multigravidas with singleton pregnancies attending the antenatal clinics, delivering at the facilities, and consenting to participate in the study were recruited.

It was preferred to use “pregnancy-related hypertension” to include all spectra of hypertension (such as gestational hypertension, preeclampsia, HELLP (Hemolysis, elevated liver enzyme, and low platelets) syndrome, imminent eclampsia, and eclampsia) developing during pregnancy. Women considered to be at a higher risk of developing pregnancy-related hypertension, such as those with a history of hypertension (in previous pregnancy, prior to pregnancy, and in the parental family), multiple pregnancies, and known cases of uterine anomalies and those with scarred uterus (prior myomectomy, uterine curettage, manual placental removal, and intrauterine device acceptors) were excluded from the study.

Women recruited were categorized into two groups: one with prior cesarean delivery and the other with earlier vaginal delivery. The number required for the study was calculated on the basis of the incidence of hypertension in pregnancy, cesarean delivery, and women with prior cesarean delivery at the hospital in the previous year, using the following formula (10):

$$n = Z^2 P(1-P)/d^2$$

where Z is the level of confidence (95%), P is the expected prevalence (15%), and d is the desired precision (3%–5%). In the reference year of 2014–2015, the overall incidence of hypertension in pregnancy was 5% and the number of women with prior cesarean delivery was 898. Number of women required was found to be 475 for each of the study groups to have 85% power and with 95% confidence interval (CI).

Eligible consecutive multigravida (parity score 1 and above) with prior cesarean delivery consenting to participate in the study were recruited for the study at or after 20 weeks of pregnancy. Age- and parity-matched multigravida with only a prior vaginal delivery were enrolled as controls for that case presenting within 1 week of recruiting the index case. All women were followed up until discharge from the hospital after delivery.

Willing multigravidas were informed about the study, and written consent was obtained. The study was approved by the Institutional Scientific and Ethics Committee.

Blood pressure (BP) was recorded by different people following recruitment and at every antenatal visit until discharge from the hospital after delivery using the standard protocol (11). Hypertensive disorders in pregnancy were diagnosed according to the diagnostic criteria and the severity descriptions suggested by the Task Force on Hypertension in Pregnancy (12). Hypertension was diagnosed when new-onset persistent high BP was recorded after 20 weeks of pregnancy. Raised BP was considered to be persistent

when systolic pressure was equal to or greater than 140 mm Hg or diastolic pressure was equal to or greater than 90 mm Hg on two occasions at least 4 h apart. Preeclampsia was considered to be present if new-onset sustained hypertension was associated with new-onset significant proteinuria (protein excretion ≥ 300 mg/24-h urine collection) and severe if new-onset persistent hypertension was high (systolic BP ≥ 160 mmHg or diastolic pressure ≥ 110 mm Hg) or associated with any of the following complications of new onset like: thrombocytopenia (platelet count, $< 100,000/\text{mL}$), renal insufficiency (serum creatinine concentration of 1.1 mg/dL or doubling of creatinine concentration), impaired liver function (elevated blood concentrations of liver transaminases to twice the normal level), pulmonary edema, or cerebral or visual symptoms irrespective of proteinuria.

Body mass index (BMI) was calculated by dividing weight (in kilogram) by the square of height (in meters). The weight and heights recorded at the first antenatal visit in the first trimesters were taken for calculating a woman's BMI. Height was measured on a wall-mounted fixed scale in centimeters and the weight was measured using a calibrated spring weighing machine.

Pregnancy was considered to be well-dated and reliably good when the woman was sure of her last menstrual date, had regular menstrual cycles of 28–30 days, and had first trimester ultrasound biometry corresponding to the menstrual age (13).

The primary outcome was the development of pregnancy-related hypertension: hypertension alone, preeclampsia, and severe preeclampsia in women with prior vaginal or cesarean delivery. The prevalence of each risk factor was compared between women with and without prior cesarean delivery.

Statistical Analysis

For statistical analysis, the chi-square test with Fischer's exact probability test was used for nominal data, and the Student t test was used for continuous data. A p -value of < 0.05 was considered to be statistically significant. Each confounding factor was weighted using likelihood ratios for developing hypertension. Linear regression modeling technique was used by entering all variables at the same time to carry out multivariate analysis. All the statistical analyses were performed using the statistical software package Statistical Package for the Social Sciences version 17.0 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago, IL, USA).

Results

During the study period, there were 6,587 deliveries in the study hospitals. Among them, 1,345 were the ones with prior cesarean delivery. Pregnancy hypertension was present in 721 women (10.9%).

The factors that are thought to influence the outcome, such as age, BMI, birth interval from previous delivery, and neonatal birth weights, were found to be comparable between prior cesarean and vaginal delivery groups. Parity/gravidity was comparable. The proportion of women with different body weight categorization was comparably distributed among the two study groups. There were no women in the category of obesity class 2 and 3. Even the distribution of women with birth interval between index pregnancy and the immediate past pregnancy were comparable between the two study groups.

The most common indication for prior cesarean delivery was non-reassuring fetal status (30.8%), and 13.5% women did not have a record to suggest this indication. Although there were 12 women with oligohydramnios and one with a small-for-dates baby, the former had babies heavier than 2,500 g and the latter had no associated oligohydramnios (Table 1).

A total of 108 women developed hypertension (11.9% of 950 study women). The proportion of women developing hypertension was significantly higher among those with prior cesarean delivery (16% vs. 6.7% in pregnancies with prior vaginal deliveries; $p < 0.05$) (Figure 1). The incidence of hypertension alone and preeclampsia was also significantly higher in the prior cesarean group. There were two women who had eclampsia in the prior vaginal delivery group and none in the other group (Table 2).

The proportion of women developing pregnancy-related hypertension much earlier in gestation was significantly higher in the previous cesarean group. More number of women developed hypertension before 32 weeks of pregnancy in the prior cesarean

group (19 of 76; 25% than 6 of 32; 18.7% in women with the prior vaginal delivery group; $p = 0.6468$). Even among cohorts of 32–36 weeks of pregnancy, hypertension was more common in the prior cesarean group (47 of 76; 61.8% than 18 of 32; 56.2% in women with previous vaginal deliveries; $p = 0.1963$).

Surprisingly, after 36 weeks of pregnancy, the diagnosis of hypertension was significantly higher in multigravidas with prior vaginal delivery ($p = 0.006$) (Table 3).

However, the proportion of patients with severe and not severe disease was not different in the groups studied. The occurrence of hypertension with respect to various maternal variables did not show any difference among the groups studied. The likelihood ratios for each of the maternal variables for the development of pregnancy hypertension were calculated. Prior cesarean delivery and maternal BMI of $>25 \text{ kg/m}^2$ were indicative of increase in the likelihood of hypertension, although very minimal. There was a minimal decrease in the likelihood of association with hypertension if a woman had prior vaginal delivery and was not overweight. Maternal age lesser or higher than 30 years and the duration of birth interval to index pregnancy did not show any association. There was no change if a woman had a gravidity of 3, whereas a gravidity of 2 suggested a slight decrease in the likelihood to develop hypertension (Table 4).

To study the effect of other maternal variables on the probability of influencing the occurrence of hypertension in a pregnancy in relation to prior mode of delivery, the data were subjected to

Table 1. Indications for prior cesarean delivery (N=475)

Indication	Cases (n)	Percent
Non-reassuring fetal status		30.8
• Meconium stained amniotic fluid	54	11.4
• Fetal heart trace abnormality	92	19.4
Cephalo-pelvic disproportion		13.7
• Elective cesarean	42	8.9
• Arrest of descent	18	3.8
• Obstructed labor	5	1.0
Labor abnormalities		12.6
• Failed induction	31	6.5
• Failure to progress	25	5.3
• Protracted dilatation	4	0.8
Previous cesarean delivery	25	5.3
Placenta previa; antepartum hemorrhage	40	8.4
Malpresentation		13
• Breech	61	12.8
• Transverse lie	1	0.2
Oligohydramnios*	12	2.5
Fetal growth restriction**	1	0.2
Unclear indication	64	13.5

*Only pregnancies without growth restriction were included.
 **The case with no hypertension and no oligohydramnios.

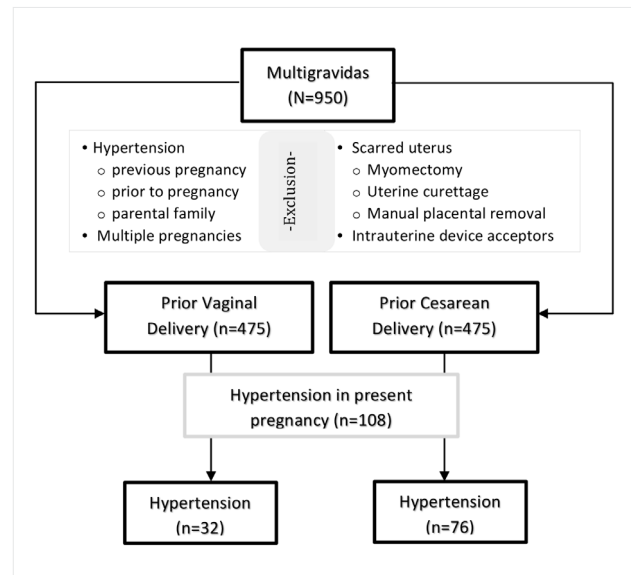


Figure 1. Design of the study

Table 2. Incidence of hypertension among the study groups

Pregnancy hypertension	Prior cesarean delivery [N=475] n (%)	Prior vaginal delivery [N=475] n (%)	Significance (chi-square)
All cases	76 (16.0%)	32 (6.7%)	$p = 0.011$
• Hypertension only	42 (8.8%)	13 (2.7%)	
• Preeclampsia	34 (7.2%)	17 (3.6%)	
• Eclampsia	-	2 (0.4%)	

Table 3. Diagnosis of hypertension and duration of pregnancy

Duration of pregnancy (weeks)	Prior cesarean delivery [N=76]	Prior vaginal delivery [N=32]	
24	-	-	
26	1	-	
28	1	1	
30	-	2	
32	17	3	
34	2	1	
36	50	16	
38	5	9	
	n (%)	n (%)	Significance (chi-square)
24–27.6	2 (2.6%)	1 (0.3%)	0.6171
28–31.6	17 (22.4%)	5 (9.3%)	0.5967
32–35.6	52 (68.4%)	17 (53.1%)	0.1963
36+	5 (6.5%)	9 (28.1%)	0.0063

multiple logistic regression analysis. None of the variables that could be studied showed any influencing effect on prior cesarean delivery for the significantly higher association with hypertension (Table 5).

Pregnancy complications were noted in both the groups studied. Proportion of pregnancies with fetal growth restriction and oligohydramnios were significantly higher in the group with prior cesarean delivery (29 and 38 to 10 and 15 of previous vaginal delivery groups; $p=0.001$). Occurrence of placental abruption ($p=0.2$) and HELLP syndrome ($p=1$) was similar in both the groups. The incidence of preterm delivery in the study groups was 11.4% overall and was higher in the prior cesarean (13.1% of 475) than in prior vaginal delivery group (9.7% of 475; $p=0.82$). Of the 950 deliveries, there were four perinatal deaths (two still births and two early neonatal deaths), and all four belonged to the vaginal delivery group. The perinatal death rate in the study group was 4.21 per 1,000 births.

Discussion

Hypertensive disorders are a major complication of pregnancy, increasing perinatal and maternal perinatal and maternal morbidity, and mortality. They occur less frequently in multigravida than in the primigravida women. Therefore, a majority of research studies have focused on nulliparous women. The incidence of hypertension in subsequent pregnancies in the present study was noted to be 11.9%. When compared to that among all women during the study period in the study population, the incidence of hypertension was on the higher side (10.9% of 6,857 deliveries). The reason for it could be that this was a case-control study and there were equal number of women in both the study groups. The proportion of normal multigravida who developed pregnancy hypertension was 6.7% of 475 women. This was lesser than the overall incidence of 10.9% of 6,587 deliveries in the study population during the study period.

Table 4. Proportion of women with hypertension in relation to influencing variables (N=108)

Maternal variables	Prior cesarean delivery [N=76] (n, %)	Prior vaginal delivery [N=32] (n, %)	Significance (chi-square)
Severity of hypertension			
Not severe	42 (56%)	20 (62.4%)	$p=0.0667$
Severe	34 (44%)	12 (37.5%)	
Age (y)			
20–25	39 (51.3%)	14 (43.8%)	$p=2.398$
26–30	23 (30.2%)	11 (34.4%)	
≥31	14 (18.4%)	7 (21.8%)	
Parity			
Gravida 2	64 (84.2%)	23 (71.8%)	$p=0.685$
Gravida 3	12 (15.7%)	9 (28.1%)	
BMI (kg/m²)			
<18.5	5 (1.1%)	1 (0.2%)	$p=1.666$
18.5–24.9	31 (6.5%)	13 (2.7%)	
25–29.9	28 (5.9%)	14 (2.9%)	
>30	12 (2.5%)	4 (0.8%)	
Birth interval (months)			
<18	3 (3.9%)	1 (3.1%)	$p=3.808$
18–48	46 (60.5%)	11 (65.6%)	
>48	27 (35.5%)	10 (31.3%)	

BMI: body mass index

Table 5. Likelihood and odds ratio for the development of hypertension

Variable	Likelihood		OR	
	Likelihood ratio	95% CI	OR	95% CI
Prior cesarean delivery	1.49	1.29–1.71		
Prior vaginal delivery	0.56	0.42–0.76		
Age < 30 y	0.56	0.42–0.76	0.987	0.55–1.77
Age, >30 y	0.96	0.87–1.05		
Gravidity 2	0.87	0.79–0.96	1.3	0.858–2.02
Gravidity 3	1	0.7–1.42		
BMI, <25 kg/m ²	0.58	0.48–0.71	0.318	0.55–1.21
BMI, >25 kg/m ²	1.23	0.81–1.86		
Birth interval, ≥18 months	0.86	0.80–0.93	0.183	0.053–0.633
Birth interval, <18 months	0.61	0.50–0.72		
Birth weight	-	-	0.778	0.313–2.386

BMI: body mass index

It may be argued that the inclusion of women who underwent surgery for oligohydramnios and a woman with a small-for-gestational age baby in the study group could have been avoided because these conditions, oligohydramnios and small-for-date gestation may be the manifestation of utero-placental insufficiency and may suggest an underlying pathology for hypertension. The patients with oligohydramnios included those who had given

birth to babies heavier than 2,500 g and one woman who gave birth to a small-for-gestational age baby had the normal amniotic fluid index, with no features of growth restriction. It can be presumed that they did not have utero-placental insufficiency sufficient enough to influence the risk status to develop hypertension in the study pregnancy.

The main objective of the study was to determine whether there is an association between prior cesarean delivery and occurrence of hypertension in subsequent pregnancies. At the time of recruitment, women at a higher risk for the development of hypertension were excluded and the variables such as age, gravidity/parity, BMI, and birth intervals were equally distributed among the study and control groups of prior cesarean and vaginal delivery. The occurrence of hypertension was significantly higher [16% vs. 6.7%, $p=0.01$; odds ratio (OR), 2.9] in prior cesarean multigravidas. The multivariate analysis did not reveal any influence of the confounding variables on this higher incidence of hypertension and suggested prior cesarean as the possible independent factor responsible for pregnancy hypertension.

Evaluating the impact of prior cesarean section on preeclampsia risk in a subsequent pregnancy, Cho et al. (9) in their Korean Registry-based study found the risk of preeclampsia in any pregnancy to be 2.17%, that in the first pregnancy to be 2.76%, and in the second pregnancy to be 1.15%. They noted that in the entire population, prior cesarean section was associated with preeclampsia risk in their subsequent pregnancy (OR, 1.26; 95% CI, 1.13–1.41) and concluded that cesarean section in the first pregnancy was associated with increased preeclampsia risk in the second pregnancy.

Similarly, examining obstetric outcomes in the second birth in women who had undergone a previous cesarean delivery in a hospital-based retrospective cohort study, Laveriano and Redondo (14) found that women with previous cesarean delivery were more likely to have preeclampsia (OR, 1.4; 95% CI, 1.2–1.6).

To assess the possible effects of a cesarean delivery on the outcome in subsequent pregnancies, Daltveit et al. (15) analyzed 637,497 first and second births among women with two or more single births and 242,812 first, second, and third births among women with three or more single births registered in the population-based Medical Birth Registry of Norway between 1967 and 2003. They reported that compared with a vaginal delivery at first birth, a prior cesarean delivery followed increased risks of preeclampsia (OR, 2.9; 95% CI, 2.8–3.1) in the second pregnancy.

The results from the present study and the concurring reports of the authors cited above (14, 15) provide us with a risk evaluation method for pregnancy-related hypertension in the second pregnancy following cesarean delivery. It assumes a greater significance and importance because it is known that the frequency of resorting to cesarean delivery is on the rise all over the world (16-21) as well as in India (22-24).

The reason for increasing incidence of hypertension in pregnancies following cesarean delivery or in women with scarred uterus could be revascularization of the uterine tissue because of impaired implantation, and placental development due to scarring. Blood flow to the uterus and placenta is demonstrated to be affected as a result of fibrosis and scar formation (25). Uterine scarring was

reported to be associated with certain biochemical changes. Reduced pan-transforming growth factor-beta 3 levels and connective tissue growth factors, and a slight increase in tumor necrosis factor levels were noted (26).

These evidences and reports of associations between prior cesarean delivery and hypertension in subsequent pregnancy make obstetricians stringently follow the indications for primary cesarean delivery. It enables one to view the practice of cesarean delivery on demand more closely, and these reports help counseling prospective mothers.

It is important to emphasize that prior cesarean delivery is a risk factor for hypertension and that hypertension manifested in them much earlier in pregnancy. One-fourth of the women with prior cesarean delivery who developed hypertension were less than 32 weeks' pregnant, and this proportion was higher when compared with women with prior vaginal delivery developing hypertension in their subsequent pregnancy. In addition, the proportion of women with severe disease remained high, with nearly more than one-third of the women with hypertension being severe (hypertension or preeclampsia without proteinuria) in either of the groups. It is possible that the observation in more number of cases may show a significant association worthy of clinical significance. Although the findings are not significant, the observations suggest that when hypertension occurs in multigravida, more of the women affected will have severe forms of the disease and that early-onset hypertension is more common in those with prior cesarean deliveries.

Although the women with known risk variables for hypertension were excluded, in the study groups, there were factors such as age, BMI, parity, and time since last cesarean delivery that could have influenced the occurrence of hypertension in the prior cesarean group as they were not considered in calculating the sample size required to be studied. The results showed that BMI characteristics were similar and comparable between the studied groups and that the study groups should have also been matched for their BMI. Larger cohorts with these variables may help in arriving at a definitive inference to implicate cesarean scar as the possible risk factor.

Excluding the women with known risk factors of developing hypertension and choosing the matched controls with respect to age and parity, analysis of the data to negate the influence of unsuspected variables in interpretation using multivariate logistic regression model can be taken as the strengths of the study.

It can be concluded that pregnancy-related hypertension is more common in women with prior cesarean delivery and when it occurs onset of hypertension is at an earlier weeks in pregnancy. In multigravida, severe forms of the disease are more common.

Etik Komite Onayı: Bu çalışma için etik komite onayı Manipal Üniversitesi Kasturba Tıp Fakültesi'nden alınmıştır, Mangalore (IEC KMC MLR 12-14/288 tarihli 17 Aralık 2014).

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - P.K.; Tasarım - P.K., D.S.D.K.; Denetleme - P.K.; Veri Toplanması ve/veya İşlenmesi - D.S.K.D.; Analiz ve/veya Yorum - D.S.D.K., P.K.; Literatür Taraması - D.S.K.D.; Yazıyı Yazan - P.K.; Eleştirel İnceleme - P.K.; Diğer - P.K., D.S.D.K.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kasturba Medical College, Manipal University, Mangalore (IEC KMC MLR 12-14/288 dated 17 December 2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.K.; Design - P.K., D.S.D.K.; Supervision - P.K.; Data Collection and/or Processing - D.S.K.D.; Analysis and/or Interpretation - D.S.D.K., P.K.; Literature Search - D.S.K.D.; Writing Manuscript - P.K.; Critical Review - P.K.; Other - P.K., D.S.D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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