The Effect of Vitamin E and Vitamin C on the Prevention of Preeclampsia and Newborn Outcome: A Case–Control Study

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Abstract

Aims and Objectives This study was undertaken in order to study the combined effect of vitamin C and E supplements during pregnancy on the incidence of preeclampsia and to study its effect on neonatal outcome.

Materials and Methods This study was conducted in Goa Medical College, from March 2010 to June 2011. Cases and controls were taken randomly from antenatal patients

attending our hospital OPD. The study group included 200 pregnant women in second trimester (13 weeks onwards) and third trimester of pregnancy. Cases included 100 women who receive oral vitamin C in dose 500 mg and oral vitamin E in dose of 400 IU per day. Control group included 100 women who did not receive vitamin E and vitamin C. All women were advised not to take any other multivitamin supplements.

Conclusion The incidence of preeclampsia in this study was 7 % in cases and 13 % in controls. Twenty out of the total 200 antenatal patients had developed preeclampsia. There was a 46 % risk reduction in the incidence of preeclampsia in cases as compared to controls. The incidence of severe preeclampsia in cases was 2 % and in controls was 7 %. This result showed 72 % reduced risk in the development of severe preeclampsia in cases as compared to controls. The study showed that significant number of antenatal patients developed preeclampsia in the age group 25–30 years, more so in controls. Primigravidas were at greater risk of developing preeclampsia than

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multigravidas in our study. The primigravidas in control group showed 36 % increased risk of developing preeclampsia as compared to cases. Out of 20 patients, 6 of them developed preeclampsia before 34 weeks and 14 patients developed preeclampsia after 34 weeks. There were more preterm deliveries in non-vitamin group as compared to vitamin-supplemented group. There was 46 % reduced risk in occurrence of preterm deliveries in vitamin-supplemented group, and this result was statistically significant. There was 50 % reduction in risk of stillbirths and neonatal deaths in vitamin-supplemented group, but this result was not statistically significant. The incidence of neonatal admissions was 10 % in cases and 16 % in controls. Hence, it is seen that there was 53 % reduced risk of neonatal admissions in cases, and this result was statistically significant. Controls were 1.26 times more prone for LSCS as compared to cases. Hence, we recommend routine vitamin C and E intake in all pregnant women, starting from 13 weeks of pregnancy onwards till delivery.

Keywords Preeclampsia · Antioxidants · Vitamin C · Vitamin E

Introduction

Preeclampsia is much more than hypertension and proteinuria. It is a syndrome virtually affecting every organ system. The identification of preeclampsia and its effective management plays a significant role in the outcome of pregnancy both for mother and baby.

Prevention of preeclampsia would mean a significant step forward in prenatal care. If preeclampsia is a state of oxidative stress, supplementation of antioxidants is likely to reduce the incidence or minimize the disease state.

Aims and Objectives

1. To study the combined effect of vitamin C and E supplements during pregnancy on the incidence of preeclampsia.
2. To study the effect of vitamin C and E intake in pregnant women and on newborn outcome.

Materials and Methods

This study was conducted in Goa Medical College, from March 2010 to June 2011 after the approval from the ethical committee. Cases and controls were taken randomly

from antenatal patients attending our hospital OPD. The study group included 200 pregnant women in second trimester (16 weeks onwards) and third trimester of pregnancy.

Inclusion criteria included: singleton pregnancy and age group between 18 and 40 years.

Exclusion Criteria

Multiple pregnancy, age below 18 years and above 40 years, patients having other medical disorders, patients with previous 2 or more LSCS.

Cases included 100 women who receive oral vitamin C in dose 500 mg and oral vitamin E in dose of 400 IU per day. Control group included 100 women who did not receive vitamin E and vitamin C. All women were advised not to take any multivitamin tablets.

Observation

Observation of relative benefit on incidences of preeclampsia and newborn outcomes in both groups were made. Preeclampsia was diagnosed with BP 140/90 mmhg, 6 h apart and urine albumin of >1+ or 24-h urine protein >300 mg/24 h [1]. Gestational age at which preeclampsia was diagnosed was noted. Also whether it was mild or severe preeclampsia was noted. Subgroups with risk factors such as previous history of preeclampsia and eclampsia, diabetes mellitus, obesity and chronic hypertension were compared in both cases and control groups.

All women who were detected to have preeclampsia underwent investigations like hemoglobin, renal function, liver function, serum electrolytes, serum uric acid, 24-h urine protein, fundus tests, and ultrasound for fetal surveillance; weight charts and growth charts were maintained.

Those controlled on diet and antihypertensive drugs and without complications were admitted at 37 weeks of gestation. Those who developed complications were managed in hospital from time of diagnosis under strict and close observations.

Antenatal cases and controls either had a spontaneous delivery or required induction of labor, augmentation of labor or cesarean section. All deliveries were attended by neonatologists, and records of neonatal complications were kept. The maternal and fetal outcomes were compared in both groups, and the recorded data were statistically analyzed by using Chi-square test. All observations are given in form of tables.

Observation Tables

	Cases	Controls	RR (95 % CI)	<i>p</i> value
Incidence of preeclampsia	7	13	0.54 (0.33–0.87)	<0.05
No preeclampsia	93	87		
Mild preeclampsia	5	6	0.79 (0.42–1.46)	>0.05
No preeclampsia	93	87		
Severe preeclampsia	2	7	0.28 (0.12–0.63)	>0.05
No preeclampsia	93	87		
Preeclampsia patients of <34 weeks	2 (28 %)	4 (30 %)	0.93 (0.33–2.6)	>0.05
Preeclampsia patients of >34 weeks	5 (72 %)	9 (70 %)	1.03 (0.36–3.8)	>0.05
Gestational age of delivery <37 weeks	12	22	0.54 (0.37–0.79)	<0.05
>37weeks	88	78		
Birth weight <2.5 kg	8	142	0.57 (0.35–1.08)	>0.05
Preterm births	12	22	0.54 (0.37–0.79)	<0.05
Still births	1	3	0.5 (0.14–1.72)	>0.05
Neonatal death	2	4	0.5 (0.44–1.09)	>0.05
Low Apgar	5	7	0.71 (0.39–1.2)	>0.05
Admission in NICU	10	16	0.47 (0.31–0.70)	>0.05
Vaginal delivery	78	62	1.26 (1.01–1.7)	<0.01
LSCS	22	38		

	Cases		Controls		RR (95 % CI)	<i>p</i> value
	Total	Preeclampsia	Total	Preeclampsia		
Age distribution in years						
18–24	36	2 (5.5 %)	30	1 (3.0 %)	2.03 (0.57–7.13)	>0.05
25–30	22	2 (9.0 %)	26	9 (34 %)	0.26 (0.11–0.66)	<0.05
31–35	35	3 (8.5 %)	38	2 (5.2 %)	1.63 (0.63–4.18)	>0.05
>35	7	0 (0 %)	6	1 (16 %)		
Parity						
Primigravida	56	4 (7 %)	53	11 (20 %)	0.36 (0.19–0.66)	<0.05
Multigravida	44	3 (7 %)	47	2 (4.2 %)	1.6 (0.62–4.08)	>0.05
BMI						
<30 kg/m ²	68	3 (4.4 %)	65	5 (7.6 %)	0.58 (0.27–1.2)	>0.05
>30 kg/m ²	32	4 (12.5 %)	35	8 (22.8 %)	0.55 (0.28–1.06)	>0.05
Risk factors						
Chronic hypertension	2	0	3	1 (33 %)		
BMI > 30 kg/m ²	32	4 (12.5 %)	35	8 (22.8 %)	0.55 (0.28–1.06)	>0.05
DM	4	1 (25 %)	5	2 (40 %)	0.62 (0.14–2.75)	>0.05
Previous eclampsia, preeclampsia	4	3 (75 %)	3	2 (66 %)	1.13 (0.21–6.19)	>0.05
Multiple risk groups	2	1 (50 %)	3	2 (50 %)	1 (0.15–1.5)	>0.05

Discussion

The above study was conducted in GMC in the Department of Obstetrics and Gynaecology, during the period from March 2010 to June 2011. Cases were 100 women with

singleton pregnancies receiving 500 mg vitamin C and 400 IU vitamin E per day from 12 weeks gestation till term. Controls consisted of 100 patients with singleton pregnancies, who did not receive the vitamin C and E supplements.

Incidence

It was noted that, out of 100 women in the case group, 7 % developed preeclampsia, 5 % of which developed mild preeclampsia and 2 % developed severe preeclampsia. In the Control group, out of 100 women, 13 % developed preeclampsia, 6 % of which developed mild preeclampsia and 7 % developed severe preeclampsia.

There is 46 % reduced risk of developing preeclampsia in patients taking vitamin E and C in our study, as the relative risk is 0.54, (95 % confidence interval 0.33–0.87), p value <0.05. This is suggestive of statistically significant risk of developing preeclampsia in control or non-vitamin group. Similar studies conducted worldwide showed less incidence of preeclampsia among vitamin-supplemented group:

Studies	Year	Incidence in cases (%)	Incidence in control (%)	Relative risk (CI)	p value
VIP [2]	2006	15	16	0.97 (0.80–1.17)	>0.05
Beazley [3]	2003	17.3	18.8	0.92 (0.40–2.13)	>0.05
Chapell [4]	1997	8	17	0.46 (0.24–0.91)	<0.05
Sharma [5]	2003	2.9	6	0.48 (0.24–0.97)	<0.05
RIVAS [5]	2000	1.2	16.6	0.07 (0.01–0.54)	<0.05

Significant risk of developing preeclampsia in non-vitamin group is seen in Chapell 1999, Sharma 2000 and Rivas 2000 studies [4, 5].

Following studies showed increased incidence of preeclampsia in cases than controls but the risk is not statistically significant.

Studies	Year	Incidence in cases (%)	Incidence in controls (%)	Relative risk (CI)	p value
ACTS [6]	2006	6	5	1.20 (0.82–1.75)	>0.05
INTAPP [7]	2010	5.9	5.7	1.04 (0.75–1.44)	>0.05

Development of mild preeclampsia is not significant, in both groups in our study. RR 0.79, (95 % CI 0.42–1.46), p value >0.05, is observed. This involves a 21 % reduction of risk in development of mild preeclampsia in case group, but this is not statistically significant. There is a 72 % reduced risk of developing severe preeclampsia in case

group, RR 0.28 (95 % CI 0.12–0.63), p value <0.05, suggesting statistical significance.

No statistical significance is seen in the studies mentioned below, though the incidence of severe preeclampsia is more in controls.

In VIP trial 2006, 5 % cases and 4 % controls developed severe preeclampsia, RR 1.17 (95 % CI 0.82–1.68) [2]. In Beazley 2003, 6.3 % cases and 5.7 % controls developed severe preeclampsia, RR 1.08 (95 % CI 0.23–5.11) [3]. In VIP trial 2006, 10 % developed mild preeclampsia in cases and 11 % in controls, RR 0.9 (95 % CI 0.57–1.4).

Age

The present study revealed that there is significant risk in developing preeclampsia in the age group 25–30 years in both cases and controls. The incidence of preeclampsia in cases is 9 % and in controls is 34 %, RR 0.26 (95 % CI 0.11–0.66), p value <0.05. Though, the overall incidence of preeclampsia in cases is more in this subgroup of 25–30 years, there is 74 % reduced risk of developing preeclampsia in cases as compared to controls in this subgroup, which is statistically significant. VIP Trial 2006, Chapell 1997, ACTS trial 2006 and South African trial (A.M Gulmezoglu et al.) 1997 showed most cases of preeclampsia in both groups between 25 and 30 years [2, 4, 6, 8].

Parity

In our study, we observed that 7 % primigravidas and 7 % multigravidas among cases developed preeclampsia, while 20 and 4.2 % preeclampsia were observed in primigravidas and multigravidas, respectively, in control group. There is significant risk in developing preeclampsia in primigravidas in control group, RR 0.36 (0.19–0.66), p < 0.05. This means that there is 64 % reduction in risk of developing preeclampsia in vitamin-supplemented group as compared to non-vitamin group in primigravidas.

Multigravidas were 1.6 times more at risk of developing preeclampsia in vitamin-supplemented group as compared to those not receiving vitamins. However, this result is not statistically significant. Studies showing development of preeclampsia in primigravidas with no statistically significant risk of preeclampsia in either group:

	Cases (%)	Controls (%)	RR (95 % CI)
VIP 2006 [2]	50	51	0.98 (0.75–1.29)
Chapell 1997 [4]	61	65	0.94 (0.70–1.25)

Prepregnancy BMI

No statistically significant risk of preeclampsia in subgroup of BMI $> 30 \text{ kg/m}^2$ is seen in both cases and controls. 12.5 % of cases in obese group developed preeclampsia. Though there is 45 % reduction in risk of developing preeclampsia in obese patients receiving vitamin supplementation, this result is not statistically significant. Studies in BMI $> 30 \text{ kg/m}^2$ subgroup, developing preeclampsia but showing no statistical significance:

	Cases (%)	Controls (%)	RR (95 % CI)
VIP 2006 [2]	10	12	0.87 (0.59–1.3)
Klemmenson 2009 [9]	5.7	6.3	0.90 (0.76–1.20)

Chronic hypertension

In our study, two patients in cases had chronic hypertension, but none developed preeclampsia. In control group, three patients had chronic hypertension, one developed preeclampsia. This result was not statistically significant. Studies showing patients with chronic hypertension developing preeclampsia:

	Cases (%)	Controls (%)
VIP 2006 [2]	23	22
Chapell 1997 [4]	5	7

Diabetes mellitus

Four patients in case group had diabetes mellitus, out of which 1 developed preeclampsia. Three patients in control group had diabetes mellitus, out of which two developed preeclampsia. Hence, our study showed no significant risk of preeclampsia in both groups in patients with diabetes mellitus, RR 0.62 (95 % CI 0.14–2.75). Studies showing patients with diabetes mellitus subgroup, developing preeclampsia but showing no statistical significance:

	Cases (%)	Control (%)	RR (95 % CI)
VIP 2006 [2]	19	16	1.18 (0.64–2.18)
Chapell 1997 [4]	2	1	2 (0.57–6.8)

Previous History of Preeclampsia/Eclampsia

Our observations showed 75 % patients in cases with previous history of preeclampsia/eclampsia developed preeclampsia in present pregnancy. While 66 % patients in controls with previous history of preeclampsia/eclampsia developed preeclampsia. RR is 1.13 (95 % CI 0.21–6.19), showing no significant risk of developing preeclampsia in either groups. Studies showing development of preeclampsia in patients with previous history of preeclampsia/eclampsia:

	Cases (%)	Controls (%)	RR (95 % CI)
VIP 2006 [2]	18.9	18	1.05 (0.73–1.5)
ACTS 2006 [6]	23	23	1.0 (0.73–1.36)

Multiple Risk Factors

Multiple risk factors included obesity, previous history of preeclampsia and eclampsia, diabetes mellitus and chronic hypertension. In this subgroup, 50 % developed preeclampsia in both cases and controls, RR 1 (0.15–1.15), showing no statistical significance. In VIP trial¹⁹⁶, 22 and 20 % developed preeclampsia in this subgroup in cases and controls, respectively, RR 1.1 (95 % CI 0.75–1.4). Hence no statistical significance was noted in our study as well as VIP trial.

Gestational Age at Development of Preeclampsia

In this study, 28 % patients in cases developed preeclampsia before 34 weeks and 72 % developed after 34 weeks. While in control group, 30 % developed preeclampsia before 34 weeks and 70 % after 34 weeks. The RR of developing preeclampsia in both cases and controls before 34 weeks is 0.93 (95 % CI 0.33–2.6), which means there is 7 % reduction in risk of developing preeclampsia in subgroup < 34 weeks. This result is not statistically significant. The RR of developing preeclampsia in cases and controls after 34 weeks is 1.03 (95 % CI 0.36–2.8), with no significance.

In ACTS trial, 0.7 and 0.6 % developed preeclampsia before 34 weeks in cases and controls, respectively, RR 1.18 (95 % CI 0.4–3.48), with no statistical significance. 5.2 and 4.4 % developed preeclampsia after 34 weeks in cases and controls, respectively, RR 1.2 (95 % CI 0.8–1.8), with no statistical significance [6].

Gestational Age at Birth

Preterm deliveries (<37 weeks) occurring in cases and controls in various studies are shown below:

Studies	Cases (%)	Controls (%)	RR (95 % CI)
Beazley 2003 [3]	38	29	1.32 (0.75–2.31)
Chapell 1999 [4]	4.2	3.5	1.12 (0.38–3.87)
Poston 2006 [2]	29	27	1.08 (0.95–1.21)
ACTS 2006 [6]	6.8	6.7	1.02 (0.73–1.43)

Above studies showed no statistical significance:

Steyn 2002 [5]	50 %	35 %	1.43 (1.03–1.99)
INTAPP 2010 [7]	5.97 %	3.03 %	1.97 (1.32–1.98)

In above studies, statistical significance in vitamin groups is seen suggestive of more preterm deliveries occurring in patients taking vitamin C and E.

Our study showed 12 and 22 % risk of preterm delivery in cases and control groups, respectively, RR 0.54 (95 % CI 0.37–0.79), p value <0.05. This is suggestive of statistical significance, and there is 46 % reduced risk of developing preterm deliveries in vitamin-supplemented group as compared to non-vitamin group in contrast to the above-mentioned studies.

Birth Weight

Eight percentage of cases and 14 % of controls had babies with birth weights <2.5 kg, RR 0.56 (95 % CI 0.35–1.08). Though more low-birth-weight babies were born in non-vitamin group and there was 44 % reduced risk of low birth weight babies in vitamin-supplemented group as compared to non-vitamin group, p value >0.05 which means that this result was not statistically significant.

Studies showing low-birth-weight babies:

Studies	Cases (%)	Controls (%)	RR (95 % CI)
INTAPP 2010 [7]	1.54	1.25	1.23 (0.62–2.43)
ACTS 2006 [6]	8.7	9.9	0.87 (0.66–1.16)
VIP 2006 [2]	28	24	1.15 (1.02–1.3)
Beazley 2002 [3]	3.8	8.3	0.46 (0.09–2.41)
Sharma 2003 [5]	12	23	0.51 (0.29–0.91)

The VIP trial and INTAPP trial showed slightly more low-birth-weight babies in vitamin-taking group, but this result is not statistically significant. The Sharma 2003 study showed significant risk of developing low-

birth-weight babies in control group not taking vitamins [2, 5, 7].

Mode of Delivery

Seventy eight percentage patients taking vitamin C and E delivered vaginally and 22 % delivered by LSCS in case group in our study. In control group, 62 % delivered vaginally and 38 % delivered by LSCS. RR is 1.26 (95 % CI 1.01–1.7), Chi-square value being –6.09 for degree of freedom 1, p value <0.01, suggestive of statistically significant rate of LSCS in controls than cases. This means that there is 1.26 times more chance of LSCS in control group.

Studies	RR (95 % CI) for vaginal deliveries
Beazley 2002 [3]	2 (0.51–7.78)
Rumbold 2006 [6]	1.10 (0.98–1.24)

No statistical significance noted in above studies:

Studies	RR (95 % CI) for LSCS
Rumbold 2006 [6]	1.02 (0.87–1.18)

No statistical significance is observed in above study. Of the 100 patients in each group, in the control group 13 patients had a previous LSCS, while in the case group 15 patients had a previous LSCS, thus there was no statistical significance between the two groups. Patients with 2 or more previous LSCS were excluded. Most of the LSCS in our study were done on emergency basis for indications like fetal distress, previous LSCS with CPD and failure to progress. Fetal distress was associated with low-birth-weight babies and preterm deliveries which were more in control groups.

Stillbirths

One percentage cases and 3 % controls had stillbirths in our study. The RR is 0.5 (95 % CI 0.14–1.72), with no statistical significance being observed.

Studies showing risk of stillbirths:

	Cases (%)	Controls (%)	RR (95 % CI)
ACTS 2006 [6]	0.9	0.6	1.34 (0.47–3.86)
VIP 2006 [2]	3	2	1.62 (0.92–2.86)
South African [8]	26	31	0.65 (0.34–1.26)

Above studies also showed no statistical significance.

Neonatal Deaths

In our study, 2 % cases and 4 % controls had neonatal deaths. RR was 0.5 (95 % CI 0.44–1.09), p value >0.05 , and no statistical significance was noted, though deaths were more in non-vitamin group. Neonatal deaths were attributed to intrapartum asphyxia, respiratory distress syndrome and sepsis.

Studies showing risk of neonatal death:

	Cases (%)	Controls (%)	RR (95 % CI)
ACTS 2006 [4]	0.1	0.4	0.25 (0.1–0.54)
INTAPP 2010 [7]	1.69	0.78	2.2 (1.02–4.73)
Poston 2006 [2]	5.9	8.7	0.67 (0.28–1.64)
Steyn 2002 [5]	2.2	3.2	0.69 (0.12–4.03)

No statistical significance seen in above studies.

INTAPP study showed slightly more deaths in cases than controls, but risk was not statistically significant.

Low Apgar Score

Our study showed 5 % babies having low Apgar score (<7 at 1 min) in cases and 7 % in controls, RR 0.71 (95 % CI 0.39–1.2). This means that there is 29 % reduced risk of developing low Apgar score in vitamin-supplemented group, though there is no statistical significance of this result as the p value is >0.05 .

Studies showing risk of occurrence of low Apgar score:

	Cases (%)	Controls (%)	RR (95 % CI)
Poston 2006 [2]	5.7	6.4	0.89 (0.34–2.29)
ACTS 2006 [6]	3.2	3.2	1.0 (0.2–4.96)

Above studies also showed no statistical significance.

NICU Admissions

NICU admissions were because of preterm deliveries, low birth weights, intrapartum asphyxia and respiratory distress syndrome.

Ten percentage in cases and sixteen percentage in controls had NICU admissions, RR 0.47 (95 % CI 0.31–0.70), indicating that there is 53 % reduced risk of NICU admissions in vitamin-supplemented group as compared to non-vitamin group, and this result is statistically significant, p value <0.05 . More NICU admissions were seen in controls due to more preterm deliveries in control group.

Studies showing NICU admissions:

	Cases (%)	Controls (%)	RR (95 % CI)
ACTS 2006 [6]	1	1.6	0.6 (0.27–1.37)
VIP 2006 [2]	14	13	1.07 (0.86–1.34)
South African 1997 [8]	25	30	0.71 (0.3–2.29)

In above studies, no statistical significance was seen.

Conclusion

The following conclusions were derived at the completion of this study:

1. The incidence of preeclampsia in this study was 7 % in cases and 13 % in controls. Twenty out of the total 200 antenatal patients, who followed up and delivered in the hospital in the study period, had developed preeclampsia.
2. There was a 46 % risk reduction in the incidence of preeclampsia in cases as compared to controls, and this result was statistically significant.
3. The incidence of severe preeclampsia in cases was 2 % and in controls was 7 %. This result showed 72 % reduced risk in the development of severe preeclampsia in cases as compared to controls.
4. The study showed that significant number of antenatal patients developed preeclampsia in the age group 25–30 years, more so in controls.
5. Primigravidas were at greater risk of developing preeclampsia than multigravidas in our study. The primigravidas in control group showed 36 % of increased risk of developing preeclampsia as compared to cases, and this result was statistically significant.
6. Subgroups of patients with various risk factors in cases and controls were observed for development of preeclampsia, except for subgroup of patients with previous history of preeclampsia and eclampsia, and rest of the three subgroups had more incidence of preeclampsia in controls than cases but none were statistically significant.
7. Out of 20 patients, 6 of them developed preeclampsia before 34 weeks and 14 patients developed preeclampsia after 34 weeks.
8. There were more preterm deliveries in non-vitamin group as compared to vitamin-supplemented group. There was 46 % reduced risk in occurrence of preterm deliveries in vitamin-supplemented group, and this result was statistically significant.
9. Fourteen low-birth-weight babies were born in control group and 8 low-birth-weight babies were born to cases, but this result was not statistically significant.

10. There was 50 % reduction in risk of stillbirths and neonatal deaths in vitamin-supplemented group, but this result was not statistically significant.
11. The incidence of low Apgar score in babies was more in controls as compared to cases, but it had no statistical significance.
12. The incidence of neonatal admissions was 10 % in cases and 16 % in controls. Hence, it is seen that there was 53 % reduced risk of neonatal admissions in cases, and this result was statistically significant.
13. Controls were 1.26 times more prone for LSCS as compared to cases, and this result was statistically significant.

Hence, we recommend routine vitamin C and E intake in all pregnant women.

Compliance with ethical standards

Conflict of interest Dr. Pia Muriel Cardoso and Dr. Sushama Surve declare that they have no conflict of interest.

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2008.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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