Original Article

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Comparison of the Effectiveness of Single and Double Surface Light Emitting Diodes Phototherapy and Intensive Compact Fluorescent Phototherapy in the Treatment of Neonatal Hyperbilirubinemia

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Abstract

Aim: In newborns with extremely high serum total bilirubin levels, the phototherapy method that reduces serum total bilirubin levels most rapidly should be applied to reduce the need for exchange transfusions and thus prevent the development of acute and/or chronic bilirubin encephalopathy. The aim of this study was to compare the efficacy of single or double light-emitting diode (LED) and intensive compact fluorescent tube (CFT) phototherapy in the first 4 hours of treatment for hyperbilirubinemia.

Methods: The study was a retrospective analysis of prospectively collected data, and designed as a single-center, cross-sectional study. Sixty newborns born between 35 and 42 weeks of gestation and treated with intensive phototherapy were included in the study. Total serum bilirubin (TSB) levels were measured 4 hours after the initiation of treatment in neonates who received LED or CFT phototherapy, and the efficacy of these methods was compared.

Results: The rate of decline in TSB was 1.07 mg/dL/h in CFT, 0.74 mg/dL/h in double LED, and 0.44 mg/dL/h in single LED phototherapy. Compact fluorescent tube and double LED phototherapy were found to be more effective than single LED phototherapy ($p<0.01$, $p<0.01$).

Conclusion: In neonates with hyperbilirubinemia, intensive CFT or double LED phototherapy in the first few hours of treatment may reduce the risk of bilirubin encephalopathy.

Keywords: Neonatal jaundice, phototherapy, hyperbilirubinemia

Introduction

Sixty percent of newborns develop jaundice in the first week of life. Extremely high levels of total serum bilirubin (TSB) can create toxic effects on the central nervous system and cause permanent neurological sequelae. Infants at risk of severe hyperbilirubinemia must be identified early and followed closely (1,2). The standard of care for pathologic hyperbilirubinemia is phototherapy. Phototherapy is initiated when the TSB level reaches the treatment thresholds determined on the basis of the infant's postnatal age, gestational week, and potential risk factors for bilirubin neurotoxicity. In infants born after 35 weeks, phototherapy decisions are made using Bhutani nomograms (3,4).

The efficacy of phototherapy depends on the dose and wavelength of light used, as well as the surface area of the infant's body exposed to it, the rate of bilirubin production, and the duration of exposure to light (5). The main mechanism of action is the absorption of light photons by bilirubin molecules, resulting in the photooxidation of bilirubin and the production of structural isomers (EZ-/EE-cyclobilirubin), which are excreted in bile and urine (6). Phototherapy is delivered using different devices worldwide. Conventional phototherapy uses a wavelength of 430-490 nm at an irradiance of 8-10 $\mu V/cm^2/nm$,

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whereas intensive phototherapy uses a wavelength of 460-490 nm at an irradiance of 30-40 μV/cm^2/nm (7). Conventional phototherapy is delivered using compact fluorescent light, a fiber-optic mattress, or halogen lamps. Conventional phototherapy irradiates a limited surface area of the body, causes overheating, and is less effective. Compact fluorescent tube (CFT) phototherapy is a conventional but intensive type of phototherapy. In recent years, light-emitting diode (LED) phototherapy has become an increasingly popular modality for intensive phototherapy. The American Academy of Pediatrics (APA) and the Turkish Neonatal Society (TND) recommend the use of devices with a minimum spectral irradiance of 30 μV/cm^2/nm for intensive phototherapy (2,5). A Cochrane meta-analysis (2011) concluded that LED and conventional phototherapy reduced TSB levels at similar rates (8).

The present study compared the efficacy of single or double LEDs versus intensive (CFT or tunnel) phototherapy during the first few hours of treatment in neonatal pathologic hyperbilirubinemia. The aim of this study was to identify the method of phototherapy that lowered bilirubin levels the fastest with a view to reducing the need for exchange transfusion, thus preventing the development of acute and/or chronic bilirubin encephalopathy.

Methods

Compliance with Ethical Standards

The present study was a retrospective analysis of prospectively collected data, and designed as a single-center, cross-sectional study and. It was approved by the Local Ethics Committee of Tekirdag Namik Kemal University (approval no: 2020.153.06.15, date: 18.06.2020). All procedures were prepared in accordance with the ethical standards of the institutional and/or national research committee and the 1975 Declaration of Helsinki.

Study Design

The study was conducted between July 2018 and July 2020 and enrolled 66 newborns born between 35 and 42 weeks of gestation who received intensive phototherapy and did not undergo exchange transfusion in the first 4 hours of treatment. Two patients were excluded from direct hyperbilirubinemia, one patient for cyanotic congenital heart disease, and three patients for blood culture-positive neonatal sepsis. The study was conducted with 60 infants. Decisions for intensive phototherapy and/or exchange transfusion were made on the basis of APA and TND recommendations for the approach to neonatal jaundice (2,5). Allocation into CFT, double, and single LED phototherapy was performed using randomization. Infants included in the study received CFT (20 patients), double LED (20 patients), or single LED (20 patients) phototherapy. The serum total bilirubin reduction rates of different phototherapy treatment methods in all groups were compared. Intensive phototherapy was used as the standard of care until the TSB level fell 5 mg/dL below the exchange transfusion limit. The intensity of phototherapy was reduced when TSB levels approached the phototherapy limit, and because the devices were not standardized for rates of subsequent decline in bilirubin, the total duration was not included in the study. The flow chart of the study is shown in Figure 1.

Infants were excluded if they were born before 34 weeks of gestation or after 42 weeks of gestation, underwent phototherapy using devices with different models, underwent exchange transfusion within the first 4 h, had congenital anomalies and syndromes, blood culture-positive neonatal sepsis, congenital metabolic diseases, cyanotic heart diseases, direct hyperbilirubinemia, or UDP-glucuronosyltransferase deficiency.

A number of variables were recorded, including gestational week, birth weight, sex, mode of delivery, first day of hospitalization, blood type of mothers and infants, direct Coombs test, complete blood count, thyroid function tests, liver and kidney function tests, and biochemical examinations, including serum electrolytes, serum albumin, complete urinalysis, reducing substances in urine, and TSB/DSB levels. Patients considered for hemolysis additionally underwent reticulocyte counts and peripheral smears, complemented with tests for glucose 6-phosphate dehydrogenase, pyruvate kinase, and minor blood groups in the mother or infant when needed.

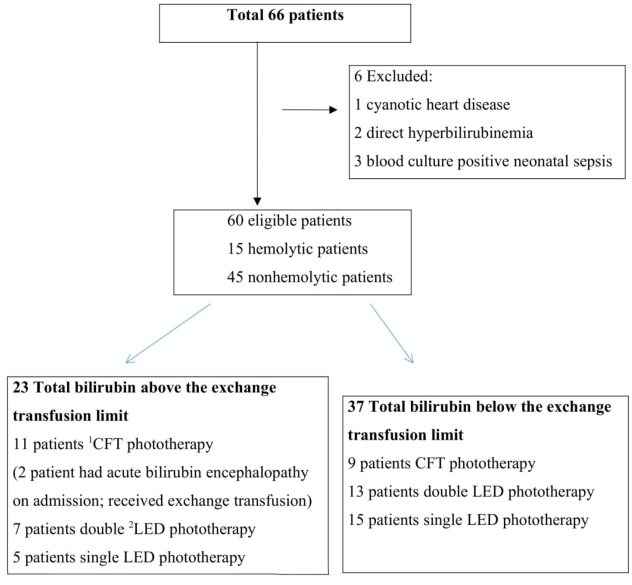

Figure 1. The flowchart of the study
[1]CFT: Compact fluorescent tube, [2]LED: Light emitting diode

Four hours after the initiation of intensive phototherapy, TSB/DSB and hematocrit levels were measured using peripheral venous blood samples. Infants with hemolytic jaundice received standard intravenous immunoglobulin (IVIG) at 0.5 g/kg at 12-hour intervals within the first 24-48 hours postnatally if the efficacy of intensive phototherapy was not sufficient and if the TSB level was close to or above the exchange transfusion limit.

Acute bilirubin encephalopathy was evaluated using the bilirubin-induced neurologic dysfunction (BIND) score (9). A BIND score of 7 was considered advanced acute bilirubin encephalopathy and prompted a decision for an exchange transfusion. Patients who were highly likely to require exchange transfusions were immediately started on intensive phototherapy while waiting for hospitalization procedures, neurological assessment scores, laboratory tests, preparation of exchange transfusion supplies, and erythrocyte irradiation procedures (irradiation can be performed outside the province).

Phototherapy

Infants received intensive phototherapy naked and in the supine position, with eyes covered with eye protectors and genitals covered with diapers. Single-surface LED phototherapy was delivered using a single device placed above the incubator, and double-surface LED phototherapy was delivered using two devices of the same brand with an overhead and lateral panel. The position was changed from the supine to the prone position every 2 hours so that phototherapy could also be applied to the back. In the CFT method, phototherapy was delivered at 360° to the whole body surface, with the patient placed on a transparent hammock. During intensive phototherapy, patients were fed orally for 15 minutes every 3 hours. The phototherapy distance varied according to the size of the baby in the incubator or tunnel but was at 30-35 cm. The efficacy of phototherapy (rate of decline of bilirubin) was evaluated using the formula pre-treatment TSB-post-treatment TSB/total elapsed time (hours). Phototherapy was discontinued when the TSB value fell below 2 mg/dL below the phototherapy limit according to the Bhutani nomogram, and rebound bilirubin levels were monitored. Before discharge, all infants underwent a brainstem auditory response test (ABR hearing screening).

Phototherapy Devices

Single or double LED phototherapy devices were equipped with high-intensity blue lamps, whereas the CFT phototherapy device was equipped with 16 white fluorescent lamps designed to surround the patient at 360°. The CFT has a thermoelevation system that activates the fan adjustment depending on the increase in ambient temperature. The level of irradiance of intensive phototherapy delivered to the infant was measured using a spectroradiometer (Macam PR450, Scotland, serial no. 8136, phototherapy radiometer). To this end, the irradiance of the light delivered to the forehead, umbilicus, and feet of the patients was measured and averaged. The features of the phototherapy devices are given in Table 1.

Statistical Analysis

Statistical analysis was performed using the SPSS 18 software. The variables were tested for normality of distribution (Kolmogorov-Smirnov and Shapiro-Wilks), followed by descriptive analyses. Normally distributed data were processed using parametric tests, and non-normally distributed data were processed using non-parametric tests. The chi-square test was used to compare categorical variables, whereas parametric continuous variables were compared using the One-Way ANOVA test. Statistical significance was set at $p<0.05$.

Results

The groups had no statistically significant differences in terms of mean gestational week, birth weight, day of initiation of phototherapy, gender, or method of delivery (Table 2).

Table 1. Features of light emitting diode and intensive compact fluorescent tube phototherapy devices

Product feature	Tende babyblue (LED[1])	Novos bilisphere 360 (CFT[2])
Type of product	LED phototherapy	Fluorescent tube phototherapy
Brand	Tende	Novos
Led phototherapy device type	High intensity	High intensity
Source of light	24 blue LEDs emitting light in a narrow band of 460 nm	420-480 nm 16 fluorescent lamps
Irradiance	120 mw/cm^2/nm	120 mw/cm^2/nm
Optimum operating distance	40 cm	30-40 cm
Phototherapy irradiance on the infant's surface area (mw/cm^2/nm)	Single LED: 83.5 Double LED: 101	78.6
Total time of use of the device (in hours)	694	746

[1]LED: Light emitting diode, [2]CFT: Compact fluorescent tube

Table 2. Demographic characteristics of the groups				
Characteristic	**CFT[1] (n=20)**	**Double LED[2] PT (n=20)**	**Single LED [3]PT (n=20)**	**p-value**
Gestational week	38±1.2 (36-40)	37.7±1.2 (35-40)	37.6±1.8 (35-41)	0.65*
Birth weight (grams)	3187±394 (2500-3950)	3162±678 (1750-4340)	3110±488 (1900-3980)	0.89*
Male sex	13 (65%)	11 (55%)	11 (55%)	0.76**
Late preterm	2 (10%)	3 (15%)	5 (25%)	0.43**
Normal spontaneous vaginal delivery	11 (55%)	8 (40%)	9 (45%)	0.62**
Time of initiation of phototherapy (days)	4.2±3.6 (1-12)	5.1±3.2 (1-11)	3.1±1.9 (1-7)	0.13*
[1]CFT: Compact fluorescent tube, [2]LED: Light emitting diode, [3]PT: Phototherapy, *One-Way ANOVA, **chi-square test				

The most common causes of pathologic indirect hyperbilirubinemia were hemolytic anemia (12 ABO and 3 Rh incompatibility) in 15 (25%) patients, neonatal dehydration/feeding problems in 23 (38%) patients, cephalic hematoma in 11 (18.3%) patients, and late preterm delivery in 10 (16.6%) patients. Four patients had urinary tract infections, 2 had maternal diabetes, 2 had suspected sepsis, and 1 had polycythemia. Investigations were normal in six (10%) patients and failed to identify any pathologic cause of jaundice. Ten (16.6%) patients had multiple risk factors.

Of the 23 infants with TSB values above the exchange transfusion limit, 11 received CFT phototherapy, 7 received double LED, and 5 received single LED phototherapy. In two patients in the CFT group who had acute bilirubin encephalopathy at the time of admission from an external center, the etiology was hemolysis. The first patient, a female baby born at 39 weeks of gestation with a birth weight of 3.050 g, had ABO incompatibility and a TSB level of 17.5 mg/dL at 8 hours after birth. Her TSB level was 17.06 mg/dL 4 hours after the initiation of intensive phototherapy (before exchange transfusion) and 9.1 mg/dL after exchange transfusion. The second patient was a female baby born at 37 weeks of gestation with a birth weight of 2.920 g. On postnatal day 4, she had a TSB level of 31.6 mg/dL, a BIND score of 8, and ABO incompatibility. Her TSB was 24.1 mg/dL 4 hours after the initiation of intensive phototherapy (before exchange transfusion) and 12.6 mg/dL after exchange transfusion. Fifty-eight infants with high TSB levels had no signs of acute bilirubin encephalopathy.

There was no difference between the groups in terms of leukocyte, hematocrit, platelet, TSB, and DSB levels before phototherapy. Post-phototherapy TSB and pre-discharge hematocrit levels were similar. Direct serum bilirubin levels before and after treatment were found to be higher in the tunnel phototherapy group than in the single LED phototherapy group (p=0.02, p=00.1). However, there was no pathological direct bilirubinemia in the patients. The mean rate of decline of TSB was 1.07±0.57 mg/dL/h with CFT phototherapy and 0.74±0.41 mg/dL/h with double LED phototherapy (Figure 2). In the first 4 hours of intensive phototherapy, CFT phototherapy decreased TSB levels by 0.33 mg/dL faster than double LED phototherapy, but the difference was not significant (p=0.06). Single LED phototherapy reduced TSB levels at a rate of 0.44±0.23 mg/dL/h. Double LED and CFT phototherapy were more effective than single LED phototherapy (p<0.01) (Table 3).

Thirteen of the 15 infants with severe hemolysis received IVIG therapy. Hearing tests were normal in all infants before discharge.

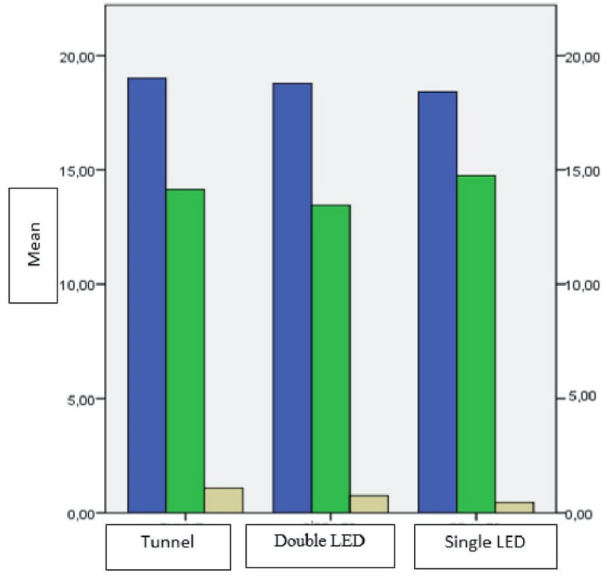

Figure 2. Pre- and post-photothreapy serum total bilirubin, rate of decline of bilirubin
LED: Light emitting diode

Table 3. Laboratory results before and after phototherapy

Parameter	[a]CFT[1]	[b]Double LED[2] PT	Single LED[3] [c]PT	p-value
Leukocytes (mm^3)	17400±11925 (8210-62460)	12540±4191 (8060-23630)	15863±10795 (6890-51350)	0.27*
Hematocrit (%)	46.2±10 (15.7-63)	48.6±8.8 (27.3-63.6)	48.8±7.7 (36-60)	0.57*
Platelets (mm^3)	305350±69455	317650±153222	270200±73205	0.34*
Pre-discharge Hematocrit (%)	42.1±11.3 (23.4-62)	44.1±10.5 (20.8-64)	44.3±7.7 (32-59)	0.55*
Albumin (gr/dL)	3.68±0.3 (3.1-4.1)	3.69±0.49 (2.3-4.2)	3.6±0.46 (2.4-4.5)	0.78*
[d]TSB[2] before PT (mg/dL)	19.0±4.35 (13.5-31.6)	18.8±2 (16.2-23.8)	18.4±2.2 (14-21.2)	0.82*
[e]DSB[3] before PT (mg/dL)	0.87±0.47 (0.21-1.88)	0.64±0.24 (0.24-1.09)	0.55±0.29 (0.18-1.31)	0.02*
TSB after PT (mg/dL)	14.2±4.2 (7.9-24)	13.46±2.75 (8.2-18.14)	14.76±2.5 (9.3-18.2)	0.45*
DSB after PT (mg/dL)	0.9±0.43 (0.2-2.1)	0.63±0.24 (0.3-1)	0.53±0.2 (0.3-1.1)	0.01*
Rate of decline of bilirubin at 4 hours of PT (mg/h)	1.07±0.57[1] (0.14-2.14)	0.74±0.41[2] (0.21-2)	0.44±0.23[3] (0.17-0.79)	[1-2]0.06* [1-3]<0.01* [2-3]<0.01*

[a]CFT: Compact fluorescent tube, [b]LED: Light emitting diode, [c]PT: Phototherapy, [d]TSB: Total serum bilirubin, [e]DSB: Direct serum bilirubin, *One-Way ANOVA (Bonferroni)

Discussion

With CFT and single/double LED intensive phototherapy, TSB levels decreased, and no acute or chronic bilirubin neurotoxicity developed. CFT and double LED phototherapy were more effective than single LED phototherapy. In intensive phototherapy, it is recommended that the surface area of the baby's skin exposed to light should be as large as possible. The surface area of the body exposed to light ranges from 35% in unidirectional LED phototherapy to 80% in multidirectional LED phototherapy. In CFT phototherapy, on the other hand, the surface area of the body exposed to light is up to 90-95% (4). This study found that single or double LED phototherapy lowered bilirubin levels at a slower rate compared with CFT phototherapy due to body surfaces not being exposed to light. The absence of any statistically significant difference between the efficacy of CFT and double LED phototherapy may be due to the low number of subjects included in the study and the relatively high number of hemolytic patients in the CFT group. This study showed that the surface area of the body exposed to light and the level of phototherapy irradiance are crucial factors determining the efficacy of conventional or LED phototherapy.

For treating neonatal hyperbilirubinemia, blue LED phototherapies provide high-intensity light with a narrow bandwidth, have a long life span, have low power consumption, and are considered the most suitable sources of light in phototherapy (10-12). While some publications have shown that LED phototherapy is more effective than conventional phototherapy, others have reported that CFT and double LED phototherapy have the same efficacy, as shown in our results. Kuboi et al. (6) showed green LED phototherapy to be as effective as blue LED in 34 patients; however, this subject has not been investigated by an adequate number of studies. Sarici et al. (13) and Uras et al. (14) reported that LED phototherapy was more effective than conventional phototherapy in non-hemolytic jaundice. Sherbiny et al. (10) investigated conventional phototherapy and super LED phototherapy and demonstrated that super LED therapy was safe, effective, and reduced the need for exchange transfusion in the treatment of hemolytic and non-hemolytic hyperbilirubinemia (super LED efficacy 87%, conventional phototherapy efficacy 64%). Takcı et al. (11) showed that CFT and LED phototherapies lowered TSB levels at similar rates in the first few hours of treatment in 43 infants with non-hemolytic hyperbilirubinemia. They reported that 4 hours after the initiation of phototherapy, the rate of decline of TSB was 0.90±0.4 mg/dL/h with CFT phototherapy and 0.78±0.4 mg/dL/h with LED phototherapy (11). Their results regarding the efficacy of phototherapy modalities are similar to our results. Kumar et al. (15) reported that LED and conventional phototherapy had equal efficacy for non-hemolytic hyperbilirubinemia in 272 neonates. Our study included subjects with hemolytic and non-hemolytic hyperbilirubinemia, and the pretreatment TSB values were higher. Differences in the results reported by previous studies may be due to the devices used in phototherapy, different etiologies of hyperbilirubinemia leading to

different rates of bilirubin production, and differences in the time of initiation and duration of phototherapy. The causes of pathologic hyperbilirubinemia in our research groups were similar to those indicated in the jaundice management guidelines (5,16).

The response to phototherapy in infants with jaundice depends on the rate of bilirubin production, the optical properties of the skin, the amount of bilirubin stored in the tissue, the level of enterohepatic circulation, and the photochemical properties of bilirubin. The most significant decrease in TSB with phototherapy occurs in the first 4-6 h of treatment. When TSB levels peak and increase the likelihood of neurological sequelae, it is essential to use the most effective and reliable modality of phototherapy (17-19). According to the manufacturer's manual, the CFT phototherapy used in our study lowers TSB levels at a rate of approximately 0.84 mg/dL/h. The higher rate of decline in TSB in patients treated with CFT phototherapy in the present study may be due to the inclusion of patients with hemolysis and TSB levels above the exchange transfusion limit. Of the patients with blood group incompatibility included in this study, 9 received CFT (7 infants with ABO incompatibility and 2 infants with RH incompatibility), 4 received double LED (3 infants with ABO incompatibility and 1 infant with RH incompatibility), and 2 received single LED phototherapy (2 infants with ABO incompatibility). The larger number of infants with hemolytic jaundice in the CFT group may have affected the results of the evaluation of the efficacy of intensive phototherapy.

The irradiance (or output) of phototherapy light delivered to the surface of the infant's skin indicates the number of photons reaching a unit area (20). According to spectroradiometer measurements in our study, the level of irradiance was 83.5 μV/cm^2/nm with single LED phototherapy, 101 μV/cm^2/nm with double LED phototherapy, and 78.6 μV/cm^2/nm with CFT phototherapy. Irradiance on the unit body surface was lower in CFT phototherapy than in single or double LED phototherapy. However, in our study, CFT phototherapy achieved the highest rate of decline in TSB, which may be related to the 360° coverage of the body surface.

Our study compared the efficacy of intensive LED and CFT phototherapy for the treatment of pathologic hyperbilirubinemia. Given that single and double LED phototherapy used the same devices, double LED phototherapy was found to be more effective as it reached a larger surface area of the body. When the TSB level was decreased below a certain level, treatment continued using a lower level of irradiance (hence a lower level of efficacy of intensive phototherapy), and that is why the total duration of phototherapy was not included in the study. This approach stems from reports associating phototherapy with transient DNA damage and concerns in recent years that phototherapy may be associated with solid tumors in childhood (21,22). Because the number of patients by hemolysis status was not equal in the phototherapy groups, subgroup analysis could not be performed for hemolytic or non-hemolytic hyperbilirubinemia.

Study Limitations

Our study was a single-center study, and patients consisted of jaundice subgroups with and without hemolysis, and the number of patients in the treatment group with jaundice above the blood exchange limit was not homogeneous. The strength of this study is that it shows that the body surface area exposed to light is crucial in determining treatment effectiveness in phototherapy methods involving traditional or LED technology.

Conclusion

This study showed that tunnel or double LED phototherapy is more effective than single LED phototherapy at high STB levels and in the first hours of treatment, and intensive phototherapy should be preferred to reduce the possibility of neurological sequelae.

Ethics

Ethics Committee Approval: It was approved by the Local Ethics Committee of Tekirdag Namik Kemal University (approval number no: 2020.153.06.15, date: 18.06.2020).

Informed Consent: This study was approved retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., B.S.T., Concept: S.T., B.S.T., Design: S.T., B.S.T., Data Collection or Processing: S.T., Analysis or Interpretation: S.T., Literature Search: S.T., B.S.T., Writing: S.T., B.S.T.

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

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