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Original Research Article

CEREBRAL OXYGENATION MONITORING DURING CORONARY ARTERY BYPASS GRAFTING AND ITS CORRELATION WITH HEMATOCRIT, MEAN ARTERIAL PRESSURE, AND PARTIAL PRESSURE OF OXYGEN IN ARTERIAL BLOOD

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ABSTRACT

Introduction: Optimal cerebral oxygenation is vital during coronary artery bypass grafting (CABG) to prevent neurological complications like cognitive decline and stroke. Non-invasive monitoring methods include near-infrared spectroscopy (NIRS), electroencephalography (EEG), and transcranial doppler (TCD). It offers real-time rSO2 assessment, detecting critical thresholds and reducing risks during cardiopulmonary bypass (CPB). **Objective:** This observational study aims to investigates cerebral oxygenation changes during CABG and correlations with hematocrit, mean arterial pressure (MAP), blood oxygen levels, CPB flows, and temperature. **Methods**: Seventy-two elective CABG patients underwent CPB with parameters including rSO2, hematocrit, MAP, PaO2, temperature, and pump flows assessed at specific time points: T1: Baseline pre-anesthesia; T2: Post-anesthesia induction (FiO2 100%); T3: Post-anesthesia induction (FiO2 50%); T4: CPB initiation; T5: CPB at 35°C; T6: CPB at 32°C; T7: CPB rewarming (36°C); T8: Post-CPB weaning (FiO2 100%); T9: Post-CPB weaning (FiO2 50%). **Results**: The mean baseline values for rSO2 were 72.14 for the right side and 71.90 for the left side. Upon initiating CPB at 35°C, a significant maximum reduction in rSO2 of 10.5% was observed, which remained below baseline during the hypothermia phase. The rSO2 values began to increase during the rewarming phase, nearly reaching baseline levels after CPB. A post hoc analysis indicated that changes in rSO2 were correlated with variations in hematocrit (correlation coefficient = 0.518), MAP (correlation coefficient = 0.399), and PaO2 (correlation coefficient = 0.001). **Conclusion:** This study explored the fluctuations in rSO2 during CABG with CPB and examined its correlations with hematocrit, MAP, PaO2, CPB flows, and temperature. The findings highlight significant correlations among these variables, providing insights into factors influencing cerebral oxygenation during cardiac surgery.

Keywords: Cardiopulmonary Bypass; Coronary Artery Bypass Grafting (CABG); Cerebral Oxygenation; Coronary artery disease; Near-Infrared Spectroscopy (NIRS)

ABSTRAK

Pendahuluan: Oksigenasi serebral yang optimal sangat penting selama operasi bypass arteri koroner atau *coronary artery bypass grafting* (CABG) untuk mencegah komplikasi neurologis seperti penurunan kognitif dan stroke. Metode pemantauan non-invasif termasuk spektroskopi inframerah dekat atau *near-infrared spectroscopy* (NIRS), elektroensefalografi (EEG), dan *transcranial doppler* (TCD). Metode ini menawarkan hasil penilaian rSO2 secara *real-time*, mendeteksi nilai ambang kritis dan mengurangi risiko selama bypass kardiopulmoner atau *cardiopulmonary bypass* (CPB). **Tujuan:** Studi observasional ini bertujuan untuk menganalisis perubahan oksigenasi serebral selama operasi CABG dan korelasinya dengan hematokrit, tekanan arteri rata-rata (MAP), kadar oksigen darah, aliran CPB, dan suhu. **Metode:** Tujuh puluh dua pasien CABG elektif menjalani CPB dengan parameter antara lain; rSO2, hematokrit, MAP, PaO2, suhu, dan aliran pompa yang dinilai pada titik waktu tertentu: T1: *Baseline* pra-anestesi; T2: Post-induksi anestesi (FiO2 100%); T3: setelah induksi anestesi (FiO2 50%); T4: Inisiasi CPB; T5: CPB pada 35°C; T6: CPB pada 32°C; T7: Pemanasan ulang CPB (36°C); T8: *Weaning* setelah CPB (FiO2 100%); T9: *Weaning* setelah CPB (FiO2 50%). **Hasil:** Nilai rata-rata *baseline* untuk rSO2 adalah 72,14 pada sisi kanan dan 71,90 pada sisi kiri. Setelah memulai CPB pada suhu 35°C, penurunan

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maksimum rSO2 sebesar 10,5% diamati, dimana tetap berada di bawah baseline selama fase hipotermia. Nilai rSO2 mulai meningkat selama fase pemanasan ulang, hampir mencapai tingkat baseline setelah CPB. Analisis post hoc menunjukkan bahwa perubahan rSO2 berkorelasi dengan variasi hematokrit (koefisien korelasi = 0,518), MAP (koefisien korelasi = 0,399), dan PaO2 (koefisien korelasi = 0,001). **Kesimpulan:** Studi ini mengeksplorasi fluktuasi rSO2 selama CABG dengan CPB dan meneliti korelasinya dengan hematokrit, MAP, PaO2, aliran CPB, dan suhu. Temuan ini menyoroti korelasi signifikan di antara variabel-variabel ini, memberikan wawasan tentang faktor-faktor yang mempengaruhi oksigenasi serebral selama operasi jantung.

Kata kunci: *Cardiopulmonary Bypass*; *Coronary Artery Bypass Grafting* (CABG); Oksigenasi serebral; penyakit arteri koroner; *Near-Infrared Spectroscopy* (NIRS)

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INTRODUCTION

Optimal cerebral oxygenation is crucial for maintaining brain function and preventing cerebral injury. The observation of cerebral oxygenation during Coronary artery bypass grafting (CABG) surgery has gained increasing attention in recent years as a means of identifying and mitigating potential cerebral oxygen imbalances. Despite progress, cerebral complications during and after CABG with Cardiopulmonary bypass (CPB) pose risks due to the brain's vulnerability to ischemic events, leading to cognitive decline, stroke, and mortality (1). A significant correlation exists between regional cerebral oxygen desaturation and neurological complications after cardiac surgery (2). Monitoring regional cerebral oxygen saturation (rSO_2) has predictive value in decreasing the incidence of early postoperative cognitive decline (3). Therefore, maintaining optimal cerebral oxygenation during CABG is crucial to alleviate these risks.

Numerous non-invasive cerebral oxygenation monitoring techniques exist, including near-infrared spectroscopy (NIRS), Electroencephalography (EEG), and transcranial Doppler (TCD) ultrasound. EEG has proven useful for early detection of imbalances between cortical tissue oxygen supply and demand (4). However, EEG monitors are not highly specific for ischemic injuries, as such imbalances are not always caused by blood flow variations (4). Other factors, such as non-convulsive seizures or prior sub-clinical traumatic cortical injuries, can also influence the readings (5). TCD complements EEG by assessing blood flow velocity in cerebral arteries, aiding in emboli detection (4). However, maintaining a stable probe position during surgery is challenging, as it involves securing the probe in place with a sterile sleeve using a band strapped around the patient's head (4). NIRS emerges as a superior alternative since near-infrared light can easily penetrate the skull, it enables real-time assessment of rSO2 using sensors placed on the patient's forehead (6). By monitoring both hemispheres, this technology can distinguish between global and unilateral causes of hypoperfusion, such as changes in head position or unilateral vessel occlusion (4). Additionally, it does not rely on pulsatile blood flow, making it particularly advantageous during cardiopulmonary bypass procedures (4). In addition to being noninvasive, NIRS has a response time of 10.9 seconds (7) about to changes in CBF. NIRS is established as a comprehensive and effective neuromonitoring modality in cardiovascular surgeries, surpassing the limitations associated with EEG and TCD.

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Interrupted blood circulation during CABG makes the brain vulnerable to ischemic incidents, manifesting as temporary impairments or severe conditions like as stroke. An rSO2 level below 45% or a decrease of 25% from individual baseline values is considered a critical threshold, indicating a higher risk of adverse neurological outcomes (6).

Numerous unresolved questions remain about the effects of hemodilution, hypothermia, and PaO2 on cerebral oxygenation. This study aimed to investigate alterations in cerebral oxygenation in patients undergoing CABG with CPB and examine potential correlations between cerebral oximetry measurements and factors such as hematocrit levels, mean arterial pressure, arterial oxygen levels, CPB flows, and temperature.

METHODS

This observational study was conducted at Swai Man Singh Medical College, Jaipur from September to December 2023, following approval from the office of the ethics committee, S.M.S. Medical College and attached hospitals, Jaipur (No. 199/MC/EC/2023 Dated 05th April 2023) and registration with the Clinical Trials Registry India (CTRI/2023/07/055738 Dated 26th July 2023). The study included adult patients scheduled for CABG with CPB under the care of a single surgeon, who met the inclusion criteria. Patients were excluded if they required emergency surgery, underwent off-pump CABG, had evidence of carotid disease, had a history of cerebrovascular accident or syncope, suffered from liver or kidney disease, acute coronary syndrome, or severe uncontrolled hypertension (MAP > 150 mmHg).

A total of 72 patients were selected for the study by purposive sampling. Upon arrival in the operating theatre, the patient's fasting status, written informed consent, and pre-anesthetic assessment results were verified. Standard routine monitors, including Non-invasive blood pressure (NIBP), oxygen saturation (SpO2) probe, and Electrocardiogram (ECG), were applied, and baseline parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and oxygen saturation) were recorded. Femoral arterial cannulation for invasive blood pressure monitoring and right internal jugular vein cannulation were performed under local anesthesia.

Two NIRS sensors (ForeSight Elite large sensor, model FSESL) were positioned bilaterally on the forehead, and rSO2 was constantly measured with the ForeSight Tissue Oximeter Monitor (Edwards Life Sciences). Measurements of rSO2R, rSO2L, hematocrit, MAP, and PaO2 were obtained at T1 [Baseline before anesthesia induction (FiO2 21%)]. Preoxygenation was conducted using 100% oxygen for a duration of 3 to 5 minutes. General anesthesia was induced with intravenous midazolam (0.05 mg/kg), fentanyl (3-5 mcg/kg), and etomidate (3-5 mg/kg). Endotracheal intubation was facilitated with intravenous rocuronium bromide (1 mg/kg), and the correct position of the tube was confirmed by 5-point auscultation and EtCO2 measurements.

Monitoring of end-tidal gases and nasopharyngeal temperature commenced post-intubation. Mechanical ventilation was configured with a tidal volume of 8 - 10 mL/kg and a 50:50 mixture of air and oxygen to achieve a PaCO2 of 35–40 mmHg. During the pre-CPB period, anesthesia was maintained with sevoflurane (1 MAC), supplemented with fentanyl (2-5 mcg/kg) and midazolam (0.05 mg/kg). Anesthesia management was maintained consistently during and after CPB

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according to institutional protocols, incorporating additional boluses of fentanyl, midazolam, and vecuronium bromide. Blood sugar levels were maintained below 180 mg/dL during the surgery in all patients.

Measurements of rSO2R, rSO2L, hematocrit, MAP, PaO_2, and CPB flows were recorded at various time points:

T1 - Baseline before anesthesia induction (FiO2 21%)
T2 - post-anesthesia induction with fio2 at 100%
T3 - post-anesthesia induction with fio2 at 50%
T4 - start of CPB
T5 - on CPB at 35°C
T6 - on CPB at 32°C
T7 - on CPB after rewarming to 36°C
T8 - post-weaning from CPB with fio2 at 100% after protamine administration
T9 - post-weaning from CPB with fio2 at 50% before sternal closure

The CPB protocol included hypothermic CPB at 32°C using a hollow fiber membrane oxygenator and a 40-micron arterial line filter, with the CPB circuit primed with 1800 ml. During CPB, FiO2 was maintained at 100% and the hematocrit at 25%. Hypothermic CPB (32°C) was initiated at flow rates of 2.5 L/min/m², pCO2 levels were controlled between 35-40 mmHg using alpha-stat management. Intravenous nitroglycerin and dobutamine were administered at dosage 0.5 and 5 µg/kg/min, respectively, during rewarming to aid in weaning from CPB. Hemoglobin levels were maintained between 8-9 g/dL post-CPB. The rewarming process to achieve a nasopharyngeal temperature of 36°C was conducted gradually, with pacing initiated if the heart rate dropped below 60 bpm. After surgery, patients were transferred intubated to the Cardiac Surgery ICU for monitoring of postoperative complications.

Statistical analysis

Continuous variables, including rSO2, MAP, hematocrit, PaO2, and CPB flows, were presented as mean ± SD. Categorical variables were reported as frequencies and proportions. Comparison of changes in continuous variables at different time points were conducted using repeated measures ANOVA (within-subject effects). Pearson's correlation coefficient was used to evaluate the relationship between continuous variables. The independent correlation of rSO2 with other parameters was determined using a generalized estimating equation within a population-averaged model. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using the trial version of SPSS 22 software.

RESULTS AND DISCUSSION

The demographic characteristics of 72 patients who underwent cardiac surgery was presented at the Table 1. The average ejection fraction was 52.33 ± 5.33%, whereas the duration for CPB and Cross-clamp was 76 ± 22 and 54.40 ± 13.5, respectively.

The initial mean rSO2 values were 72.14 ± 8.96% for the right side (rSO2R) and 71.90 ± 8.05% for the left side (rSO2L) at T1. Following intubation and administration of 100% FiO2 at T2, both rSO2R and rSO2L demonstrated a statistically significant relative increase, reaching 73.50 ± 9.17% and 73.01 ± 9.17%, respectively. However, a decline in these values was observed at T3 (50% FiO2). At T4, coinciding with the initiation of cardiopulmonary bypass (CPB) at 35°C, there was a significant decrease in both rSO2R and rSO2L.

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Table 1. Demographic profile, comorbidities, number of coronary vessels involved, Ejection fraction, medications, and CPB (N=72)

Variable	Values
Age (years) [Mean ± SD]	53.15 ± 8.05
Weight (kgs) [Mean ± SD]	62.5 ± 7.36
Body surface area (meter^2) [Mean ± SD]	1.69 ± 0.16
Gender	
Male [N (%)]	50 (69.4)
Female [N (%)]	22 (30.6)
Diabetic Patients [N (%)]	24 (33.33)
Hypertensive Patients [N (%)]	38 (52.8)
Smokers [N (%)]	32 (44.44)
History of Unstable angina [N (%)]	9 (1.25)
History of myocardial infarction [N (%)]	16 (22.22)
History of both unstable angina and myocardial infarction [N (%)]	4 (5.56)
Number of involved coronary vessels {Mean ± SD (range)}	2.5 ± 0.5(2-3)
Ejection fraction (%) [Mean ± SD]	52.33 ± 5.33
Patients taking nitrates [N (%)]	63 (87.5)
Patients taking β-blockers [N (%)]	67 (93.056)
Patients taking ACEI/ARII antagonists [N (%)]	38 (52.8)
Cardiopulmonary Bypass time (minutes) [Mean ± SD]	76 ± 22
Cross-clamp duration (minute) [Mean ± SD]	54.40 ± 13.5

During CPB (T5), both rSO2R and rSO2L reached their lowest values, with a maximum relative decrease of 10.5% observed. During hypothermia (32°C) at T6, there was a slight increase in oximetry values, which further improved during rewarming to 36°C at T7. Post-CPB (T8 and T9), oximetry values approached baseline and were not significantly different from those at T1. Both rSO2R and rSO2L exhibited comparable patterns during surgery, with minor differences noted, and no measurements dropping below the 50% threshold [Table 2].

Table 2. Variations in cerebral oximetry values (right and left), hematocrit, MAP, PaO2, and CPB flow rates throughout the surgery

Time points	rSO2R (Mean±SD)	rSO2L (Mean±SD)	Hematocrit (Mean±SD)	MAP (Mean±SD)	PaO2 (Mean±SD)	CPB Flows (Mean±SD)
T1	72.14 ± 8.96	71.90 ± 8.05	40.80 ± 6.88	84.06 ± 12.14	69.63 ± 23.29	_
T2	73.50 ± 9.17	73.01 ± 9.17	38.81 ± 7.53	85.53 ± 14.23	581.80 ± 90.68	_
T3	71.70 ± 8.83	73.71 ± 8.48	36.79 ± 8.43	83.01 ± 16.42	389.21 ± 106.68	_
T4	68.01 ± 8.56	70.50 ± 8.96	29.49 ± 5.6	70.04 ± 19.83	515.30 ± 85.37	3 ± 0.42
T5	64.59 ± 8.96	67.39 ± 9.38	27.50 ± 5.63	67.02 ± 15.46	231.15 ± 102.4	3.06 ± 0.4
T6	65.50 ± 8.78	66.71 ± 9.43	27.19 ± 6.21	67.53 ± 12.78	363.08 ± 87.04	3.02 ± 0.47
T7	66.51 ± 9.82	67.63 ± 8.71	27.09 ± 5.81	69.02 ± 15.87	507.83 ± 77.52	3.07 ± 0.45
T8	68.80 ± 9.42	71.92 ± 8.77	28.80 ± 5.38	71.52 ± 13.38	404.83 ± 66.91	_
T9	69.60 ± 10.3	73.94 ± 9.21	29.81 ± 5.75	75.01 ± 16.19	362.78 ± 99.88	_

MAP: Mean arterial pressure; **PaO$_2$**: Partial pressure of oxygen in arterial blood; **CPB**: Cardiopulmonary Bypass

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The baseline hematocrit at T1 was 40.80 ± 6.88, significantly decreasing at T3. A significant decrease occurred at T4 (36.79 ± 8.43 to 29.49 ± 5.6). No significant changes were observed in hematocrit levels at T5 to T7 during CPB. After complete rewarming at T9, hematocrit increased in comparison to T5 [Table 2]. Initially, at baseline (T1), both rSO2R and rSO2L showed a weak positive correlation with hematocrit. After the administration of anesthesia (at T2 and T3), the correlation for both rSO2R and rSO2L increased to moderate levels. During the CPB stages, which included cooling, hypothermia, and rewarming (T4 to T7), the correlations for both rSO2R and rSO2L fluctuated but showed statistically significant associations, indicating varying influences of hematocrit. Post-CPB, the correlations weakened again, highlighting minimal relationships in later stages [Figure 1].

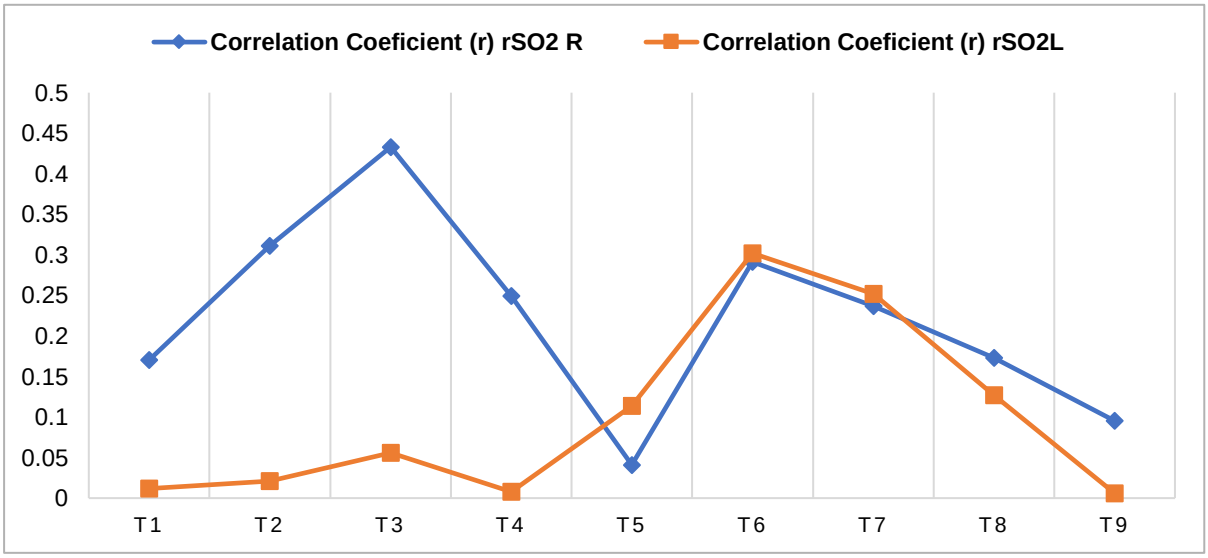

Figure 1. Trend of Pearson correlation coefficients between rSO2 and hematocrit levels (The x-axis represents the correlation coefficient values while the y-axis lists the time points from T1 through T9; **Blue Line** corresponds to the correlation trend between rSO2 on the right side (rSO2R) and hematocrit; **Orange Line** indicates the correlation trend for the left side (rSO2L) with hematocrit)

Mean Arterial Pressure (MAP) decreased significantly at T4 (70.04 ± 19.83 mm Hg) compared to the baseline value at T1 (84.06 ± 12.14 mm Hg). T5 had the lowest MAP (67.02 ± 15.46 mm Hg) during the surgical period. MAP increased from T7 and achieved 75.01 ± 16.19 mm Hg at T9 [Table 2]. Initially, at baseline (T1), both rSO2R and rSO2L showed modest positive correlations with MAP. At T2 and T3, the correlations for both rSO2R and rSO2L largely diminished, although they remained statistically significant. During the CPB process, including the cooling and hypothermia phases, the correlations varied, often showing modest strength. Notably, correlations strengthened slightly during hypothermia for rSO2R and reverted to positive for rSO2L upon rewarming. After CPB, both rSO2R and rSO2L demonstrated more pronounced positive correlations with MAP [Figure 2].

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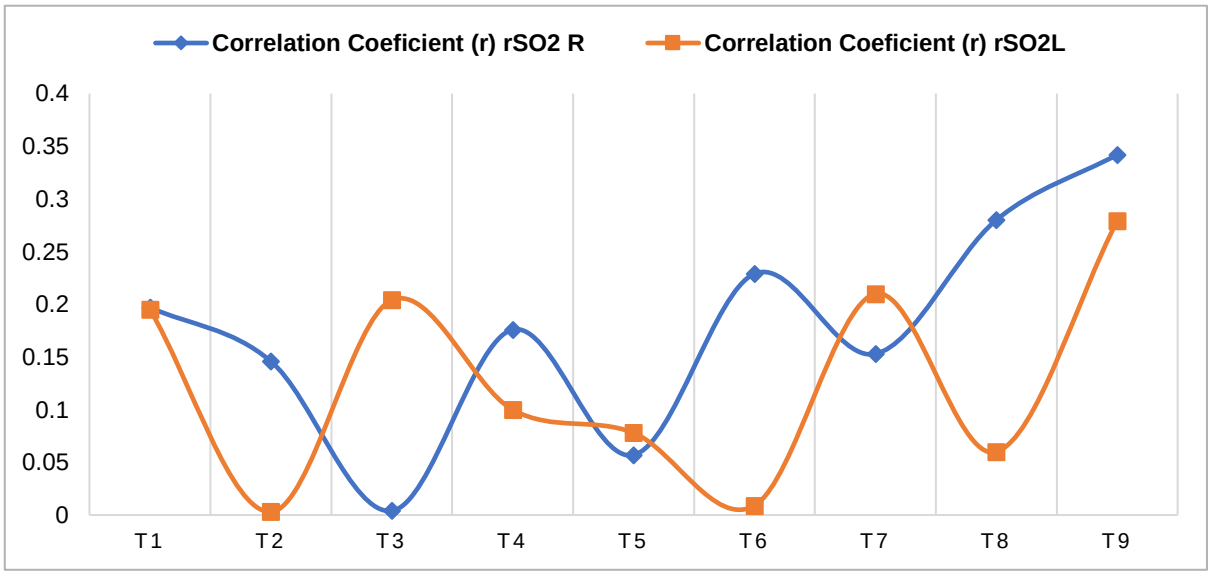

Figure 2. Trend of Pearson correlation coefficients rSO2 and MAP
(The x-axis represents the correlation coefficient values while the y-axis lists the time points from T1 through T9; **Blue Line** corresponds to the correlation trend between rSO2 on the right side (rSO2R) and MAP; **Orange Line** indicates the correlation trend for the left side (rSO2L) with MAP)

The baseline PaO2 at T1 was 69.63 ± 23.29 mm Hg, significantly increasing post-intubation (T2) to 581.80 ± 90.68 mm Hg and then decrease at T3 to 389.21 ± 106.68 mm Hg. T4 showed a significant increase, accompanied by variable values in subsequent time points. T9 exhibited a significant decrease of PaO2 compared to T8 [Table 2]. Initially, at T1, both rSO2R and rSO2L exhibited moderate positive correlations with PaO2, indicating a direct relationship between higher oxygen levels and increased cerebral oxygen saturation. Nevertheless, following the induction of anesthesia at T2 and T3, these correlations diminished for both rSO2R and rSO2L, becoming statistically non-significant, which indicates a reduced influence of PaO2 on rSO2 during these stages. During the different stages of CPB, including cooling, hypothermia, and rewarming, the correlations for rSO2R remained very weak and non-significant. Notably, rSO2L showed a moderate correlation during the cooling phase, though this did not extend to the hypothermia or rewarming phases. After weaning from CPB, both rSO2R and rSO2L showed statistically non-significant positive correlations with PaO2 [Figure 3].

Upon the initiation of CPB (T4), flows averaged 3 ± 0.42 l/min/m2. There was no significant difference in flows at T5 and during hypothermia at T6. At T7 (nasopharyngeal temperature of 36°C), CPB flows increased but were not significantly different from T5 [Table 2]. Our study identified significant correlations between hematocrit and rSO2 on the right (0.518) and left sides (0.338). Similarly, a 1 mm Hg change in MAP resulted in significant changes in rSO2R (0.399) and rSO2L (0.292). However, the correlation between rSO2 and PaO2 was weak and not statistically significant ($p > 0.05$), with rSO2R and rSO2L changing by a factor of 0.001 for every 1 mm Hg change in PaO2. This indicates the possibility of forecasting alterations in cerebral oximetry values based on variables such as hematocrit, MAP, and PaO2 [Table 3].

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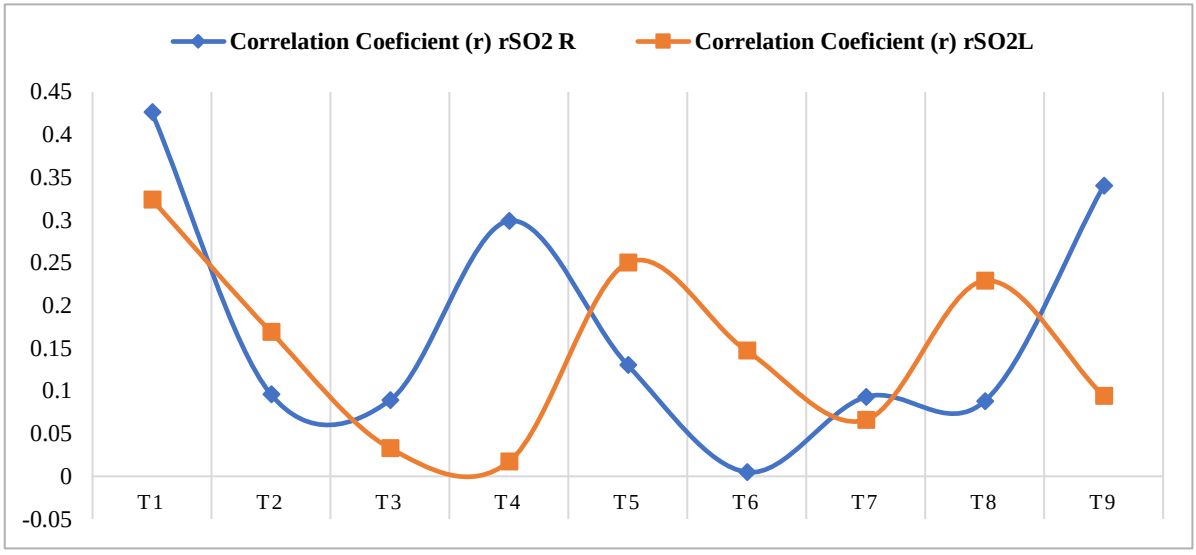

Figure 3. Trend of Pearson correlation coefficients rSO2 and PaO2
(The x-axis represents the correlation coefficient values while the y-axis lists the time points from T1 through T9; **Blue Line** corresponds to the correlation trend between rSO2 on the right side (rSO2R) and PaO2; **Orange Line** indicates the correlation trend for the left side (rSO2L) with PaO2.)

Our findings demonstrated a moderate positive correlation between rSO2 and Hematocrit on both the right (r = 0.518) and left sides (r = 0.338), with statistical significance (P < 0.001 for both sides) [Table 3]. This corresponds with several other studies highlighting the importance of hematocrit in preserving cerebral oxygenation after cardiac surgeries. Yamamoto et al., (8) established a significant correlation between hematocrit levels and cerebral oxygen saturation during both the pre-CPB and CPB phases in pediatric cardiac surgery. Similarly, in a study conducted by E.E. Ševerdija et al., (9), discovered that a decrease in hematocrit levels during CPB resulted in a significant reduction in mean cerebral tissue oxygenation. These consistent findings across multiple studies underscore the need for strategies to manage hematocrit levels during CPB, including blood transfusions, to prevent significant drops in cerebral oxygenation.

The positive correlations between rSO2 and MAP observed in our study (r = 0.399 for rSO2R and r = 0.292 for rSO2L, both P < 0.001) [Table 3] indicate that blood pressure significantly influences cerebral oxygen saturation. Numerous studies showing that adequate perfusion pressure is essential for maintaining cerebral oxygenation during surgery. Mansouri et al., (10) reported a significant relationship between MAP and cerebral oximetry in pediatric cardiac surgery, indicating that increasing MAP during CPB enhances brain perfusion and oxygenation. Pan et al., (11) analyzed 141 patients and discovered that rSO2 increased with an increase in MAP during CPB, with a correlation in children but not in neonates or infants.

We found very weak and non-significant correlations between rSO2 and PaO2 [r = 0.001 for both rSO2R (P = 0.896) and rSO2L (P = 0.792)], indicating that within the observed range, PaO2 does not exert a substantial direct influence on cerebral oxygen saturation. This finding aligns with research by Sarvesh Pal Singh et al., (12) , which identified a correlation coefficient of 0.005 between rSO2 and PaO2

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and observed minimal effects of PaO2 fluctuations on cerebral oxygenation compared to changes in MAP and hematocrit. This supports the idea that PaO2 plays a less direct role in influencing rSO2 during surgery.

Table 3. Comparison between rSO2 and various variables using a Generalized Estimating Equation (GEE) on a population-averaged model

Variable tested	Correlation coefficient	P value
rSO2R and hematocrit levels	0.518	**<0.001***
rSO2L and hematocrit levels	0.338	**<0.001***
rSO2R and MAP	0.399	**<0.001***
rSO2L and MAP	0.292	**<0.001***
rSO2R and PaO2	0.001	0.896
rSO2L and PaO2	0.001	0.792

*Based on the Wald Chi-Square test, Significant if the p-Value < 0.05
rSO2R: regional oxygen saturation on the right side of the frontal lobe; **rSO2L**: regional oxygen saturation on the left side of the frontal lobe; **MAP**: mean arterial pressure; **PaO2**: partial pressure of oxygen in arterial blood.

Baseline measurements (T1) in our study indicated consistent mean rSO2 levels of 72.14 ± 8.96% on the right side and 71.90 ± 8.05% on the left side. A study by Singh et al (12) involving 40 patients reported baseline rSO2 values of 64.35 and 64.97 for the right and left sides, respectively, whereas another study by Mohandas et al., (13) reported baseline rSO2 values of 65.78 and 66.32 for the right and left sides, respectively. The average difference between the right and left rSO2 values in our study was negligible. The non-zero difference observed could be attributed to the limited sample size. Post-intubation and exposure to 100% FiO2 (T2) significantly increased mean rSO2 (73.50 ± 9.17% on the right, 73.01 ± 9.17% on the left) despite a reduction in mean HCT (38.81 ± 7.53% from 40.80 ± 6.88). The average MAP showed a significant increase during this period. Contrary to Sarvesh Pal Singh et al., (12), who attributed an increase in PaO2 solely to this initial rise in rSO2 values, we find this explanation insufficient as increased MAP cannot be ignored according to our observation, this underscores the need for a comprehensive approach addressing multiple physiological parameters.

Upon the initiation of CPB (T4), there was significant decrease in mean rSO2 was 68.01 ± 8.56% on the right and 70.50 ± 8.96% on the left, associated with lower Hematocrit (29.49 ± 5.6%) and MAP (70.04 ± 19.83 mm Hg), despite adequate PaO2 (515.30 ± 85.37 mm Hg). During CPB (T5-T7) with hypothermia, mean rSO2 levels stabilized (64.59 ± 8.96% to 66.51 ± 9.82% on the right, 67.39 ± 9.38% to 67.63 ± 8.71% on the left), indicating adaptations to modified conditions despite fluctuating Hematocrit and MAP. Full CPB flows and reduced imbalance between cerebral metabolic oxygen consumption (CMRO2) and cerebral blood flow (CBF) during hypothermia might contribute to these adaptations.

After CPB (T8-T9), mean rSO2 approached baseline values (68.80 ± 9.42% to 69.60 ± 10.3% on the right, 71.92 ± 8.77% to 73.94 ± 9.21% on the left), which were achieved at significantly lower hematocrit and MAP compared to baseline (29.81 ± 5.75 vs 40.80 ± 6.88 and 75.01 ± 16.19 vs 84.06 ± 12.14, respectively). Higher PaO2 values post-CPB, especially with 100% FiO2, suggest an impact of PaO2 on rSO2. However, some studies have reported a decline in rSO2 during early rewarming stages. In an animal study conducted by Ostadal et al., (14), it was reported that brain oxygen saturation levels were significantly higher in the hypothermia

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group compared to the normothermia group. One possible explanation for this could be increased oxygen demand in normothermia. In their study, Moerman et al., (15) concluded that lower cerebral oxygen saturation is associated with lower flows during CPB. Enhanced CPB flows during rewarming to meet the brain's heightened oxygen requirements might account for the observed increase in rSO2 values post-full rewarming in our patients.

The findings of our study align with existing literature, emphasizing the complex interplay between hematocrit, MAP, and cerebral oxygen saturation during CABG with CPB. The moderate positive correlations between rSO2 and both hematocrit and MAP highlight their critical roles in ensuring adequate cerebral oxygen delivery and perfusion. The weak correlations between rSO2 and PaO2 indicate that while maintaining adequate PaO2 is necessary, it may not be the primary determinant of cerebral oxygen saturation.

The homogeneous patient population and exclusion criteria may limit the application to all CABG patients. Moreover, environmental factors and technology limitations may influence measurement accuracy. Although correlations were identified, causative relationships were not established, necessitating further research.

CONCLUSION

This study investigated the variations in rSO2 during CABG with CPB and analyzed its relationships with hematocrit, MAP, PaO2, CPB flows, and temperature. The findings highlight significant relationships between these variables, providing insights into factors influencing cerebral oxygenation during cardiac surgery.

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Conflict of Interest

The authors declare that there are no conflicts of interest among them.

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Author's Contributions

JS, IV, SA, and ND contributed to the study's concept and design, data collection and processing, data analysis and interpretation, manuscript drafting, and revision for significant intellectual content, and provided administrative, technical, or material support. They also contributed to the literature review and gave final approval of the manuscript for submission.

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Original Article

BISPECTRAL INDEX VERSUS MINIMUM ALVEOLAR CONCENTRATION GUIDED ANESTHESIA FOR ASSESSMENT OF INTRA-OPERATIVE AWARENESS IN PATIENTS UNDERGOING LAPARASCOPIC ABDOMINAL SURGERY

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ABSTRACT

Introduction: Intraoperative awareness with explicit recall (AWR) occurs when an individual retains memory of intraoperative events after completion of anesthesia. It is an unpleasant feeling feared by both the patients and the anesthetists. **Objective:** This research aims to compare Bispectral Index (BIS) versus Minimum Alveolar Concentration (MAC) guided anesthesia for assessment of intra-operative awareness in patients undergoing laparoscopic abdominal surgery. **Methods:** This research is a prospective comparison involving 100 patients divided into two groups of 50 patients each. Group M (MAC): Desflurane concentration was maintained at a MAC value of 1. The BIS monitor was not to be applied to this group of patients at the time of induction, but in Group B (BIS), the BIS electrode was applied on the forehead immediately before induction. Hemodynamic parameters including heart rate and mean arterial blood pressure were recorded. After the surgery, the patients were interviewed using the Modified Brice Awareness Questionnaire and Michigan Awareness Classification score for assessment of intra-operative awareness or consciousness at two intervals: in the post-anesthesia care unit and 48 hours after surgery. **Results:** Demographic data were comparable between groups M and B. No significant differences in the hemodynamic parameters, which include heart rate and mean arterial blood pressure (MAP) between the M group and the B group (p value>0.05). The patient's awareness was compared based on a modified Brice awareness questionnaire. The distribution of awareness was comparable between groups M and B (0% vs. 4% respectively) (p value=0.495). The distribution of Michigan awareness classification scores was comparable between groups M and B. Class 0 (no awareness) was 98% vs. 96% respectively, and Class 1(isolated auditory perception) of 2% vs. 4% respectively with (p value=1). **Conclusion:** This research found that BIS-guided anesthesia works just as well as MAC-guided anesthesia at keeping patients from waking up and keeping an eye on changes in their blood pressure while they are under general anesthesia for laparoscopic abdominal surgery.

Keywords: Awareness; Bispectral Index; Blood Pressure; Heart Rate; Mean Arterial Pressure; Minimum Alveolar Concentration

ABSTRAK

Pendahuluan: Kesadaran intraoperatif dengan ingatan eksplisit (AWR) terjadi ketika setelah selesainya anestesi, seseorang mengingat kembali kejadian intraoperatif. Kejadian ini merupakan perasaan tidak menyenangkan yang ditakuti oleh pasien maupun ahli anestesi. **Tujuan:** Penelitian ini bertujuan untuk membandingkan indeks bispektral (BIS) versus konsentrasi alveolar minimum (MAC) berdasarkan panduan anestesia untuk penilaian kesadaran intraoperatif pada pasien yang menjalani operasi laparoskopi abdomen. **Metode:** Penelitian ini adalah penelitian komparatif prospektif yang melibatkan 100 pasien dibagi menjadi 2 kelompok yang masing-masing terdiri dari 50 pasien. Kelompok M (MAC): Konsentrasi desflurane dipertahankan pada nilai MAC 1. Monitor BIS tidak diterapkan pada kelompok pasien ini pada saat induksi dan Kelompok B (BIS): Pada kelompok ini elektroda BIS diterapkan pada dahi tepat sebelum induksi. Parameter hemodinamik (denyut jantung dan tekanan darah arteri rata-rata) juga dicatat. Setelah pembedahan, pasien diwawancarai menggunakan Kuesioner Kesadaran Brice yang dimodifikasi dan skor Klasifikasi Kesadaran Michigan untuk penilaian kesadaran intra-operatif pada dua interval: di unit perawatan pasca-anestesi dan 48 jam setelah pembedahan. **Hasil:** Data

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demografi dibandingkan antara kelompok M dan B. Tidak ada perbedaan signifikan dalam parameter hemodinamik yang mencakup denyut jantung dan tekanan darah arteri rata-rata antara kelompok M dan kelompok B (nilai p> 0,05). Kesadaran pasien dibandingkan berdasarkan kuesioner kesadaran brice yang dimodifikasi. Distribusi kesadaran dibandingkan antara kelompok M dan B. (Masing-masing 0% vs 4%) (nilai p = 0,495). Distribusi skor klasifikasi kesadaran Michigan dibandingkan antara kelompok M dan B. Kelas 0 (Tidak ada kesadaran) masing-masing 98% vs 96%, Kelas 1 (Persepsi pendengaran terisolasi) masing-masing 2% vs 4% dengan (nilai p = 1). **Kesimpulan:** Penelitian ini menyimpulkan bahwa anestesi yang dipandu BIS sama efektifnya dengan anestesi yang dipandu MAC dalam mencegah kesadaran dan mengelola perubahan hemodinamik selama pasien menjalani operasi perut laparoskopi dengan anestesi umum.

Kata kunci: Kesadaran; Indeks bispektral; Tekanan darah; Denyut jantung; Tekanan arteri rata-rata; Konsentrasi alveolar minimum

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INTRODUCTION

Laparoscopic surgeries are widely accepted and performed due to several advantages such as decreased postoperative pain, early ambulation, shorter hospital stay, cosmetically small incision, and more cost-effectiveness. There are three elements of balanced anesthesia namely amnesia, analgesia, and areflexia, which must always be considered while providing general anesthesia to patients (1).

The element of amnesia should be addressed carefully while anesthetizing any patient. A multitude of surgical patients apprehendto the possibility of immobility, being awake, or being in pain due to inadequate anesthesia during the surgery (2). This inadequacy results in patients having awareness during anesthesia. Intraoperative awareness with explicit recall (AWR) occurs when an individual recalls intraoperative events after completion of anesthesia. It is an unpleasant feeling feared by the patients and the anesthetists, equally. It is an important cause of post-traumatic stress disorder (PTSD) for the patients following surgery and an important medico-legal liability for the anesthesiologist. Therefore, it is important to maintain adequate depth of anesthesia during the surgery (3).

General anesthetic agents suppress cortical activity; and disrupt the connectivity of cortical areas and subcortical–cortical connections in a dose-dependent manner.

Some processing of information occurs in lighter planes of anesthesia also, even though the patients are apparently adequately anesthetized. The overall incidence of intraoperative awareness with explicit recall is approximately 0.2%-2%, but maybe >40% in some high-risk surgical patients like those with caesarean section, multiple trauma, hemodynamic instability, and cardiac surgery (4,5).

Depth of anesthesia refers to the progressive depression of the central nervous system and a decreased response to noxious stimuli. Adequate depth of anesthesia is achieved when the concentration of agents is sufficient to ensure both patient comfort and successful surgery. There are various somatic and clinical parameters, and devices available for anesthetists to monitor the depth of anesthesia. The two main methods frequently used are bispectral index (BIS) and minimum alveolar concentration (MAC). MAC relates to the concentration of the inhalational anesthetic agent to a single, clinically relevant endpoint of general anesthesia. It is defined as the minimum alveolar concentration of inhaled anesthetics required to prevent response in

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50% of the subjects to a painful stimulus. When the MAC is approximately 0.3, 50% of the subjects do not respond to verbal commands (MAC awake), and maintaining the MAC more than 0.7 is said to reduce the incidence of AWR. It is thought that the end-tidal inhaled anesthetic partial pressure shows the partial pressure in the alveoli, which in turn shows the partial pressure of the anesthetic agent at the effect site, like the brain. This makes MAC reliable and useful. Thus, with the ease of measurement of the end-tidal anesthetic gas, MAC is considered a standard metric for comparing the potency of inhalational anesthetic agents (6,7).

The Bispectral Index (BIS) is a complicated number that is made up of different EEG features, such as frequency domain, time domain, and higher-order spectral features. Based on extensive clinical data, it correlates with behavioral assessments of hypnosis and sedation, regardless of the anesthetic or sedative agent used. The BIS score ranges from 0 to 100, with a target range of 40–60 recommended to prevent awareness; it also provides a reliable prediction of consciousness levels and responsiveness (8–10). This research aims to compare Bispectral Index (BIS) versus Minimum Alveolar Concentration (MAC) guided anesthesia for assessment of intraoperative awareness in patients undergoing laparoscopic abdominal surgery.

METHODS

Research Design and Sample Size

This prospective, randomized, and comparative research was performed at the Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, with approval from the institutional ethical committee on October 22nd, 2019 with the certificate number TP(MD/MS)08/2019)/IEC/ABVIMS/RMLH/672/19. The research was conducted between November 1st, 2019 and March 31st, 2021. The sample size calculation was based on the research of Alkaissi A. et al. (11) which found no cases of awareness in the BIS-guided group and 4 cases (13.8%) in the control group. Based on these figures, a minimum sample size of 49 patients per group was calculated to achieve 80% power with a 5% significance level. Thus, a total of 100 patients were included, with 50 patients in each group.

Research Participants

A hundred patients were randomly divided into two groups of 50 patients each by computer-generated random sampling. The research included 100 patients classified as American Society of Anesthesiologists (ASA) grade I and II, aged 18 to 60 years, of either sex, undergoing laparoscopic abdominal surgery. Exclusion criteria were refusal of consent, allergy to research drugs, psychosis or memory impairment, and a history of brain injury.

Research Procedures

Written and informed consent was obtained from all patients. After a thorough preoperative evaluation and investigation, patients who met the inclusion criteria were included in the research. The night before surgery, all patients received premedication with a 0.25 mg tablet of alprazolam and a 150 mg tablet of ranitidine. Upon entering the operating room, routine monitoring was initiated, including a 5-lead electrocardiogram (ECG), pulse oximetry, and non-invasive blood pressure (NIBP) measurement. Baseline vital signs, such as heart rate, systolic, diastolic, mean blood pressure, and ECG rhythm, were recorded. An 18G cannula was inserted into the dorsum of the left hand, and intravenous fluid infusion was started. Patients were then

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randomly assigned to two groups using computer-generated random numbers. Group M (MAC): Desflurane concentration was maintained at a MAC value 1. BIS monitor was not to be applied to this group of patients at the time of induction and Group B (BIS): In this group, the BIS electrode was applied on the forehead just before induction. Depth of anesthesia was BIS guided, and a BIS value of 40-60 was targeted. Desflurane concentration was titrated to keep the BIS value between the target range.

Patients received Inj. Midazolam 0.03 mg/kg and Inj. Fentanyl 2 µg/kg intravenously. Anesthesia was induced with Inj. Propofol 2 mg/kg intravenously, and 0.1 mg/kg Vecuronium bromide was given intravenously after facemask ventilation was established. Patients were ventilated with 50% oxygen, 50% nitrous oxide, and an inhalational anesthetic agent (desflurane). Intubation was carried out after 3 minutes with an appropriately sized cuffed endotracheal tube. Target end-tidal CO2 was maintained between 32-36 mm Hg. Post intubation, patients were maintained on a gas flow of 1.5 L/min (50% nitrous oxide and 50% oxygen) and an inhalational agent (desflurane). Intraoperatively, desflurane concentration was titrated as per the group chosen. Injection of Vecuronium bromide 0.01 mg/kg was given every 30 minutes. The inhalational agent was stopped at the end of skin closure and fresh gas flows were increased to 8 L/min. All patients received paracetamol 1gram intravenously 30 minutes before completion of surgery. At the completion of the surgery, neuromuscular blockade was reversed using neostigmine (0.05-0.07 mg/kg) and glycopyrrolate (0.01-0.02 mg/kg).

Intraoperative hypotension (mean arterial pressure (MAP) < 65 mmHg or less than 20% of baseline) was treated with 6 mg boluses of mephentramine, while intraoperative hypertension (MAP > 90 mmHg or more than 20% of baseline) was treated by giving intravenous nitroglycerine (0.5 -5 mcg/Kg/min). When blood pressure was not controlled after nitroglycerine, the patient was excluded from the research.

Table 1. Modified Brice Awareness Questionnaire (12)

Question asked	Immediate postoperative period	Day 2
What was the last thing you remember before going to sleep?		
What was the first thing you remember after waking up?		
Do you remember anything between going to sleep and waking up?	Yes/No	Yes/No
Did you have any dreams while you were asleep for surgery?	Yes/No	Yes/No
Were your dreams disturbing to you?	Yes/No	Yes/No
What was the worst thing about your surgery?		
Awareness		
Yes	**No**	
• If the event recalled was confirmed by the attending personnel present in the OT or investigators are convinced that the memory was real. • Unable to recall any event but memories could have been related to intra-operative events. • The answer is yes to any of the questions asked in the above interview.	• No reported awareness • The answer is no to the questions asked in the above interview.	

After the surgery, the patients were interviewed using the Modified Brice Awareness Questionnaire (12) and Michigan Awareness Classification score (13) for assessment of intraoperative awareness at two intervals: in the post-anesthesia care unit and

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48 hours after surgery. Based on the answers given, the patients were divided as having awareness or no awareness (Table 1 and Table 2).

Table 2. Michigan Awareness Classification Score (13)

Michigan awareness classification score	
Class 0	No awareness
Class I	Isolated auditory perception
Class II	Tactile perception
Class III	Pain
Class IV	Paralysis
Class V	Paralysis and Pain

The primary objective of this research was to compare the incidence of intraoperative awareness between MAC-guided and BIS-guided anesthesia. The secondary objective was to compare hemodynamic parameters, specifically heart rate and mean arterial blood pressure, in both groups.

Statistical Analysis

In the statistical analysis, categorical variables were expressed as numbers and percentages, while continuous variables were reported as mean ± SD or median. The Kolmogorov-Smirnov test was used to assess normality, and non-parametric tests were applied if normality was not met. Quantitative variables were compared between the two groups using the unpaired t-test or Mann-Whitney test, depending on the data distribution. Qualitative variables were analyzed using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant. Data were entered into an MS Excel spreadsheet, and analysis was conducted using SPSS version 21.0.

RESULT AND DISCUSSION

A total of 100 patients were included in the research. The distribution of gender was comparable between groups M and B (female: 60% vs. 50% respectively; male: 40% vs. 50% respectively) (p-value = 0.315). The distribution of ASA grade was comparable between groups M and B (Grade I: 46% vs. 48%, respectively; Grade II: 54% vs. 52%, respectively) (p-value = 0.841). The mean age was 38.86 ± 10.6 years and 36.34 ± 9.66 years in groups M and B, respectively, and the difference was not significant between the two groups in terms of age. The distribution of age was comparable between the two groups (p = 0.217) (Table 3).

Table 3. Comparison of Demographic Characteristics between Group M and B.

Variable	Group M (n=50)	Group B (n=50)	Total	p-value
Age (years)				
Mean ± SD	38.86 ± 10.6	36.34 ± 9.66	37.6 ± 10.17	0.217*
Gender				
Female	30 (60%)	25 (50%)	55 (55%)	0.315**
Male	20 (40%)	25 (50%)	45 (45%)	
ASA grade				
I	23 (46.00%)	24 (48.00%)	47 (47.00%)	0.841**
II	27 (54.00%)	26 (52.00%)	53 (53.00%)	

* Based on the independent t-test, significant if *p*-value < 0.05
** Based on the chi-square test, significant if *p*-value < 0.05

The patient's awareness was compared based on a modified Brice awareness questionnaire. The distribution of awareness was comparable between groups M and B (0% vs. 4%, respectively) (p-value = 0.495). The distribution of Michigan awareness classification score was comparable between group M and B. Class 0 (no awareness) 98% vs 96%, respectively, Class 1(isolated auditory

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perception) 2% vs. 4% respectively with (p-value = 1) (Table 4 and Table 5).

Table 4. Comparison of the Modified Brice Awareness Questionnaire between Groups M and B

Awareness	Group M (n=50)	Group B (n=50)	Total	p-value
No	50 (100%)	48 (96%)	98 (98%)	0.495*
Yes	0 (0%)	2 (4%)	2 (2%)	
Total	50 (100%)	50 (100%)	100 (100%)	

* Based on Fisher's exact test, significant if *p*-value<0.05

No significant difference was seen in heart rate (bpm) at baseline (p = 0.084), 10 minutes after intubation (p = 0.894), at skin incision (p = 0.144), at end of port placement (p = 0.098), 15 minutes after port placement (p = 0.63), 30 minutes after port placement (p = 0.974), 60 minutes after port placement (p = 0.775), at end of skin closure (p value = 0.106), 10 minutes after extubation (p = 0.244) between group M and B.

Table 5. Comparison of Michigan Awareness Classification Score between Groups M and B

Michigan Awareness Classification Score	Group M (n=50)	Group B (n=50)	Total	p-value
Class 0 {no awareness}	49 (98%)	48 (96%)	97 (97%)	1*
Class 1 {isolated auditory perception}	1 (2%)	2 (4%)	3 (3%)	
Total	50 (100%)	50 (100%)	100 (100%)	

* Based on Fisher's exact test, significant if *p*-value < 0.05

Mean ± SD of heart rate (bpm) of group M at baseline was 86.52 ± 7.66, 10 minutes after intubation was 83.8 ± 10.27, at skin incision was 78.52 ± 9.23, at end of port placement was 77.94 ± 10.4, 15 minutes after port placement, it was 77.6 ± 7.43, 30 minutes after port placement, it was 77.38 ± 7.21, 60 minutes after port placement was 78.24 ± 8.01, at the end of skin closure was 79.38 ± 8.78, 10 minutes after extubation was 82.96 ± 7.65.

Table 6. Comparison of Heart Rate between Group M and B.

Heart Rate (beats per minute)	Group M	Group B	Total	p-value
Baseline				
Mean ± SD	86.52 ± 7.66	89 ± 6.51	87.76 ± 7.18	0.084*
10 minutes after intubation				
Mean ± SD	83.8 ± 10.27	84.08 ± 10.72	83.94 ± 10.45	0.894*
At skin incision				
Mean ± SD	78.52 ± 9.23	82.16 ± 14.82	80.34 ± 12.42	0.144*
At the end of port placement				
Mean ± SD	77.94 ± 10.4	81.82 ± 12.71	79.88 ± 11.72	0.098*
15 minutes after port placement				
Mean ± SD	77.6 ± 7.43	76.68 ± 11.2	77.14 ± 9.47	0.630*
30 minutes after port placement				
Mean ± SD	77.38 ± 7.21	77.44 ± 10.57	77.41 ± 9	0.974*
60 minutes after port placement				
Mean ± SD	78.24 ± 8.01	77.52 ± 9.3	77.9 ± 8.57	0.775*
At the end of skin closure				
Mean ± SD	79.38 ± 8.78	82.64 ± 11.08	81.01 ± 10.08	0.106*
10 minutes after extubation				
Mean ± SD	82.96 ± 7.65	84.98 ± 9.49	83.97 ± 8.64	0.244*

* Based on the Independent t-tes, significant if *p*-value<0.05

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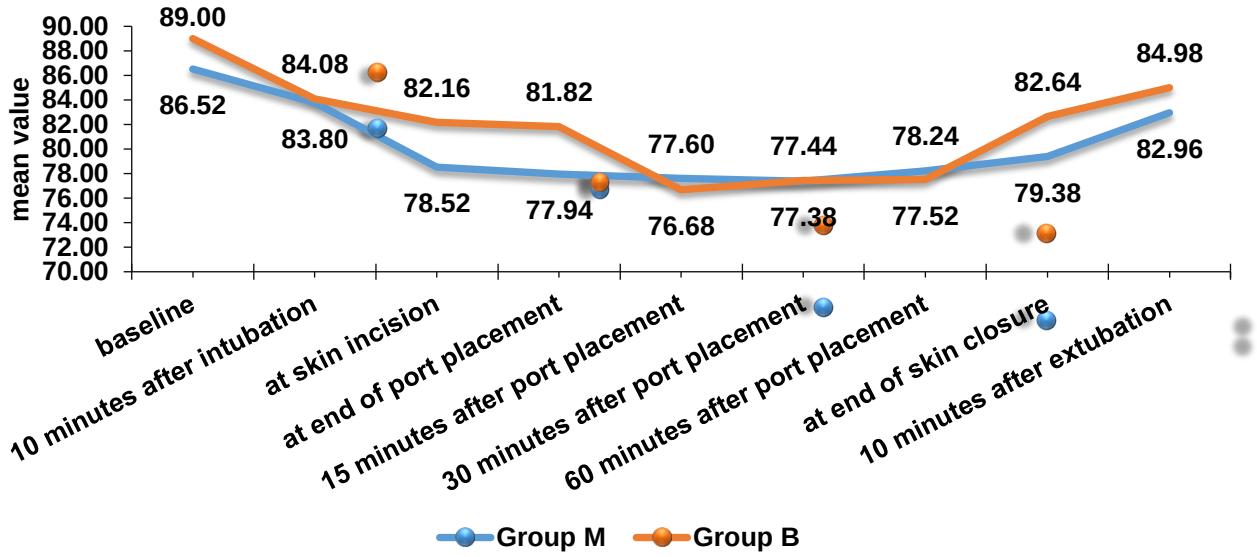

Figure 1. Comparison of The Trend of Heart Rate (Beats per Minute) at Different Time Intervals between Groups M and B.

Mean ± SD of heart rate (bpm) of group B at baseline was 89 ± 6.51, 10 minutes after intubation was 84.08 ± 10.72, at skin incision was 82.16 ± 14.82, at the end of port placement was 81.82 ± 12.71, 15 minutes after port placement was 76.68 ± 11.2, 30 minutes after port placement was 77.44 ± 10.57, 60 minutes after port placement was 77.52 ± 9.3, at end of skin closure was 82.64 ± 11.08, 10 minutes after extubation was 84.98 ± 9. (Table 6) (Figure 1).

No statistically significant difference was seen in mean arterial pressure(mmHg) at baseline (p value = 0.156), at end of port placement (p value = 0.677), 15 minutes after port placement (p value = 0.15), 30 minutes after port placement (p value = 0.654), 60 minutes after port placement (p value = 0.062), at end of skin closure (p value = 0.264), 10 minutes after extubation (p value = 0.626) between group M and B (Table 7) (Figure 2).

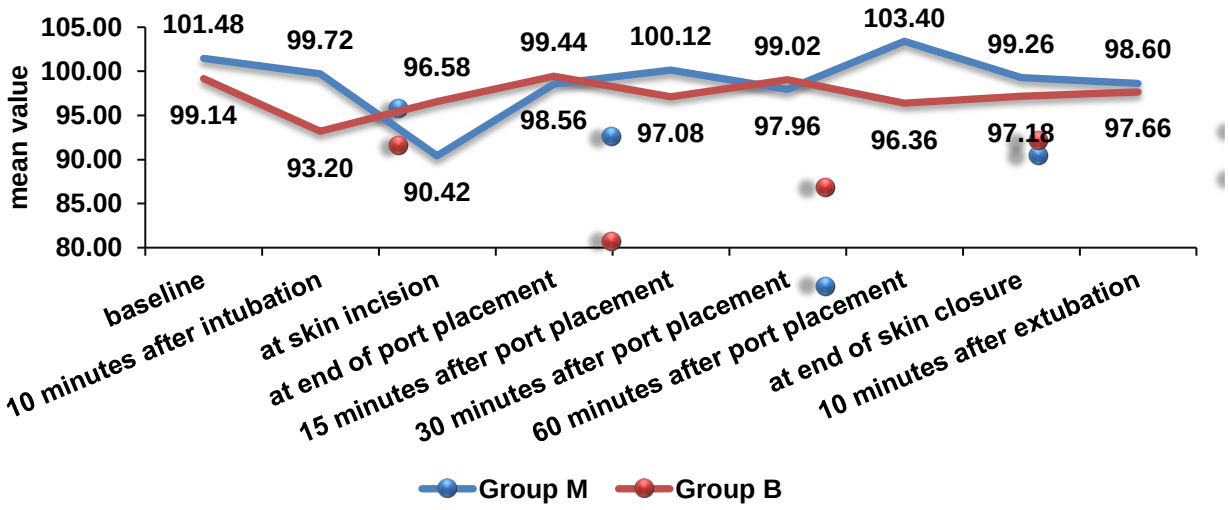

Figure 2. Comparison of The Trend of Mean Arterial Pressure (mmHg) at Different Time Intervals between Groups M and B.

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Intraoperative awareness can be a major source of post-traumatic stress disorder and cognitive dysfunction in the patients which has important medico-legal implications for the anesthesiologist.

In this research, the two groups were comparable with respect to age (P = 0.217), gender distribution (P = 0.315), and ASA physical status (P = 0.841), and no statistical difference was found between Group M and Group B. The demographic variables of age, gender, ASA grade, or type of laparoscopic surgery did not influence the incidence of intraoperative AWR nor did it affect the hemodynamic stability during the surgery. This research results of the demographic profile are in concordance with the previous research conducted by Wang J. et al. (14) and Mozafari H. et al. (15).

In this research, we observed that the incidences of intraoperative awareness in Group M and Group B were comparable with only 1 case of awareness in Group M and 2 cases of awareness in Group B (P = 1). The AWR was assessed using the Michigan Awareness Classification score. Similarly, based on the Modified Brice Awareness Questionnaire incidence of awareness in MAC and BIS-guided maintenance of anesthesia were 0% & 4%, respectively with two cases of definite intraoperative awareness reported, both being in BIS monitored group and no cases of definite or possible awareness in the MAC monitored group (p = 0.495).

The both observations are consistence with Chen Y et al. (16) which proved that the incidence rates of intra-operative anesthesia awareness were 0.62% and 0.31% in the BIS and MAC groups, respectively, and concluded that intraoperative awareness was comparable between MAC and BIS groups. The observations relating to intraoperative awareness in this research are also corroborated by the research conducted by Shanks AM et al. (17) which did not detect a difference in the incidence of definite awareness or recovery variables between monitoring protocols based on either MAC values or BIS values.

Table 7. Comparison of Mean Arterial Blood Pressure between Group M and B

Mean Arterial Pressure(mm Hg)	Group M	Group B	Total	p-value
Baseline				
Mean ± SD	101.48 ± 8.11	99.14 ± 8.27	100.31 ± 8.23	0.156*
10 minutes after intubation				
Mean ± SD	99.72 ± 10.96	93.2 ± 10.12	96.46 ± 11	0.003*
At skin incision				
Mean ± SD	90.42 ± 10.68	96.58 ± 12.99	93.5 ± 12.23	0.011*
At the end of port placement				
Mean ± SD	98.56 ± 9.78	99.44 ± 11.25	99 ± 10.49	0.677*
15 minutes after port placement				
Mean ± SD	100.12 ± 9.83	97.08 ± 11.08	98.6 ± 10.53	0.15*
30 minutes after port placement				
Mean ± SD	97.96 ± 12.51	99.02 ± 11.05	98.49 ± 11.75	0.654*
60 minutes after port placement				
Mean ± SD	103.4 ± 12.84	96.36 ± 12.25	100.11 ± 12.92	0.062*
At the end of skin closure				
Mean ± SD	99.26 ± 9.33	97.18 ± 9.2	98.22 ± 9.28	0.264*
10 minutes after extubation				
Mean ± SD	98.6 ± 8.81	97.66 ± 10.37	98.13 ± 9.59	0.626*

* Based on the Independent t-test, significant if *p*-value<0.05

The incidence of awareness was 0.12% in MAC monitored groups and 0.08% in BIS-monitored groups. In this research results are supported by the trial conducted by Mozafari H et al. (15) which showed that the overall incidence of AWR was not statistically significant in the BIS and routine monitored groups. In this research, observations were also

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supported by research conducted by Wang J et al. (14) which showed that the end-tidal anesthetic gas concentration can be used for reducing the incidence of intraoperative awareness with explicit recall. The incidence of intra-operative awareness in the MAC group was comparable to the routine monitoring group, and not statistically significant in the MAC and routine monitored groups.

This research states that there were no significant differences in the hemodynamic parameters which include heart rate and mean arterial pressure between the M group and the B group before induction, during maintenance of anesthesia and post anesthesia care unit (p value > 0.05). These results and observations are consistence with the research conducted by Mozafari H. et al. (15) who found that hemodynamic changes were not dependent on the type of technology used for monitoring the depth of anesthesia during abdominal surgeries.

The research's limitations include a small sample size and short duration, as well as recruitment exclusively from a single tertiary care hospital. To enhance precision and applicability, broader participation from multiple tertiary care hospitals would strengthen the findings. Larger sample sizes and extended research durations are necessary to yield more robust findings.

CONCLUSION

There are no significant differences in the comparison of bispectral index versus minimum alveolar concentration guided anesthesia for assessment of intraoperative awareness in patients undergoing laparoscopic abdominal surgery. Further research could explore other factors or methods to improve the assessment of intraoperative awareness during anesthesia.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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Authors' Contributions

All authors have contributed to all processes in this research.

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Original Article

A COMPARISON OF POSTOPERATIVE ANALGESIC EFFECT OF INTRAVENOUS TRAMADOL VERSUS TRANSDERMAL BUPRENORPHINE PATCH IN PATIENTS UNDERGOING AORTOFEMORAL GRAFT SURGERY

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ABSTRACT

Introduction: The popularity of the transdermal buprenorphine patch (TDB) is currently increasing for chronic pain management because of its ease of use, non-invasive nature, sustained drug delivery, and avoidance of side effects associated with oral or parenteral routes. However, its role in postoperative pain management for aortofemoral bypass surgery is poorly established. The study was designed to compare the postoperative analgesic effect of intravenous tramadol versus transdermal buprenorphine patch in patients undergoing aortofemoral graft surgery. **Objective**: To compare the efficacy between a buprenorphine patch versus intravenous tramadol for postoperative analgesia in patients undergoing aortofemoral bypass surgeries. **Methods:** This is a hospital-based, prospective, randomized, and interventional study. This study was conducted in the cardiac surgery Operation Theatre (OT). A total of 60 patients of either sex belonging to ASA 2 or 3 in the age group of 30-60 years and BMI ≤ 40 kg/m2 scheduled for aortofemoral bypass surgery were enrolled in this study. These 60 patients were divided into two groups; the intravenous tramadol and the transdermal buprenorphine patch group using a randomization table. **Results:** The two groups were comparable in terms of demographical data, duration of surgery, and time for extubation. The analysis of variance showed that the VAS score was higher in the buprenorphine group as compared to the tramadol group for the first 3 hours post operatively but after that, the VAS score was significantly less in the buprenorphine group at various study intervals. A greater number of patients complained of pain for the first 3 hours postoperatively, but after that the patients had better pain relief for the rest of the study period. **Conclusion**: Transdermal buprenorphine applied preoperatively is a safe and effective option for postoperative pain management as it offers superior pain control and reduces the need for rescue analgesia, thereby decreasing potential side effects as compared to intravenous tramadol.

Keywords: Aortofemoral Surgery; Postoperative analgesia; Rescue Analgesia; Transdermal Buprenorphine; VAS Score

ABSTRAK

Pendahuluan: Popularitas *Patch Buprenorfin Transdermal* (TDB) saat ini meningkat untuk manajemen nyeri kronis karena mudah digunakan, sifatnya yang non-invasif, pemberian obat yang berkelanjutan, dan pengurangan efek samping yang terkait dengan rute oral atau parenteral. Namun, perannya dalam manajemen nyeri pascaoperasi untuk operasi bypass aortofemoral belum ditetapkan dengan baik. Penelitian ini dirancang untuk membandingkan efek analgesik pascaoperasi tramadol intravena versus *patch buprenorfin transdermal* pada pasien yang menjalani operasi *bypass* aortofemoral. **Tujuan:** Untuk membandingkan efektivitas antara penggunaan *buprenorphine patch* versus tramadol intravena untuk analgesia pascaoperasi pada pasien yang menjalani operasi *bypass* aortofemoral. **Metode**: Studi ini merupakan studi intervensi acak berbasis rumah sakit. Studi prospektif ini dilakukan di ruang operasi bedah jantung. Sebanyak 60 pasien dari kedua jenis kelamin yang termasuk dalam ASA 2 atau 3 dalam kelompok usia 30-60 tahun dan BMI ≤ 40 kg/m2 yang dijadwalkan untuk operasi bypass aortofemoral didaftarkan dalam studi acak prospektif ini. Ke-60 pasien ini dibagi menjadi dua kelompok yaitu tramadol intravena dan kelompok patch buprenorfin transdermal menggunakan tabel pengacakan. **Hasil**: Kedua kelompok sebanding dalam hal data demografi, durasi operasi, waktu ekstubasi. Analisis varians menunjukkan bahwa skor VAS lebih tinggi pada kelompok buprenorfin dibandingkan dengan kelompok tramadol selama 3 jam pertama pasca operasi tetapi setelah itu, skor VAS secara signifikan lebih rendah pada kelompok buprenorfin pada berbagai interval penelitian. Lebih banyak pasien mengeluhkan nyeri selama 3 jam pertama pasca operasi tetapi setelah itu

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pasien mengalami pereda nyeri yang lebih baik selama sisa periode penelitian. **Kesimpulan:** Buprenorfin transdermal yang diberikan sebelum operasi merupakan pilihan yang aman dan efektif untuk manajemen nyeri pascaoperasi karena menawarkan pengendalian nyeri yang lebih baik, mengurangi kebutuhan akan analgesik penyelamatan, sehingga mengurangi potensi efek samping dibandingkan dengan tramadol intravena.

Kata kunci: Operasi Aortofemoral; Analgesia Post-operatif; *Rescue Analgesia*; Transdermal buprenorphine; Skor VAS

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INTRODUCTION

Post-operative pain management has always been a challenging issue despite our knowledge in the physiology of acute pain. Various methods of pain management exist including opioid and non-opioid analgesics, systemic and local delivery methods, and regional and minimally invasive techniques (1).

Many drugs and routes have been studied earlier. Transdermal drug delivery system plays a vital role in managing chronic as well as acute pain as they are easy to use, provide a constant rate of drug delivery, and maintain sustained blood levels for pain management. They can eliminate the need for parenteral or oral routes of drug administration, which can have side effects (2).

The buprenorphine patch is an example of a transdermal drug delivery system (TDDS) which is simple, easy to use, compliant, relatively safer, and provides sustained drug delivery. To be able to use it as a patch, buprenorphine is incorporated into an adhesive polymer matrix (acrylate vinyl acetate), which allows it to be released continuously over 7 days. The patches are available in three strengths of 5, 10 and 20 mg with drug release rates of 5, 10 and 20 mg/hour respectively (1,3).

The buprenorphine patch has been compared with oral tramadol, but till now we could not find the comparison between the buprenorphine patch and intravenous tramadol for postoperative analgesia. This study was designed with the primary aim to compare the efficacy of buprenorphine patches to intravenous tramadol for postoperative analgesia in patients undergoing aortofemoral bypass surgeries. Also, to determine the difference in time to first rescue analgesia and the total dose of rescue analgesic required in the first 72 hours postoperatively.

METHODS

This is a prospective and randomized study, that has received ethical approval from the institutional ethics committee (Ref no. 720/MC/EC/2020). The study was registered with the Clinical Trial Registry of India (CTRI) with trial number CTRI/2021/09/036226. Written informed consent was obtained from 60 patients aged 30-60 years of either sex belonging to ASA 2 or 3 with a BMI ≤ 40 kg/m2, and undergoing aortofemoral bypass surgery. There had to be 30 cases in each group to get a 95% confidence level and 80% power to confirm the expected difference of 34% in the number of cases in each group that needed rescue analgesia within 7 days, as mentioned in the seed article (4). The sample size calculation was based on the formula:

$$N = \frac{Z^2.P(1-P)}{d^2}$$

N: the sample size
Z: the level of confidence
P: the expected prevalence or proportion
d: the precision

Patients who were taking medications that may interact with tramadol or buprenorphine, alcoholics or drug abusers, and

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those who with known drug allergies were excluded from the study. The patients were divided into 2 groups either the intravenous tramadol group (Group 1) or the transdermal buprenorphine (TDB) patch group (Group 2) using a randomization table. The patients were aware of the group they belonged to (by looking at the buprenorphine patch or IV tramadol); however, the physician assessing pain and satisfaction score was unaware of the group the patient belonged to. Hence it was a single-blinded study.

The complete process about the study drugs, post-operative pain treatment options, and pain score assessment was explained to patients a day before surgery. Patients in the buprenorphine group received a buprenorphine patch of 10 mcg/h, 18 hours before the surgery (effective serum concentration is achieved after 12-24h) which was applied to the upper outer arm (4). A dosage of alprazolam 0.25 mg was given to all patients the night before surgery to allay anxiety. On the day of surgery, all the baseline parameters (heart rate [HR], blood pressure [BP], oxygen saturation [SpO2]) were recorded, and the intravenous (IV) line was secured. Before induction of anesthesia, IV glycopyrrolate (0.2 mg) and midazolam 0.15 mg/kg were administered to all patients. After preoxygenation, anesthesia was induced with IV midazolam 0.05 mg/kg, fentanyl 2 mcg/kg, etomidate 0.3 mg/kg, and rocuronium 0.9mg/kg to attempt intubation. Anesthesia was maintained with 60% of N_20 and 40% of O_2, isoflurane 1-1.5%, and atracurium 0.5 mg/kg loading dose followed by 0.1 mg/kg maintenance dose. The bispectral index score was maintained between 40-60 throughout the surgery by varying the concentration of isoflurane and 1mcg/kg fentanyl. End-tidal CO2 was kept between 35 and 40 mmHg by adjusting ventilation.

The patients in the buprenorphine group were not given any other analgesic apart from their routine buprenorphine patch, whereas patients in the tramadol group did receive 100 mg tramadol at the time of skin closure, followed by 50 mg every 6 hours till 72 hours. Postoperatively, pain (using visual analogue scores 0-10), sedation score, and hemodynamic parameters were assessed at 1, 3, 6, 12, 24, 36, 48, 60, 72 hours.

Rescue analgesia in the form of 1 gram Paracetamol up to 3 times a day was given to patients whose VAS score went 4 or higher. If in any patient, pain persisted within 6 hours of giving paracetamol then diclofenac (75 mg IM) was given as a secondary rescue analgesic. Recordable side effects were lightheadedness, postoperative nausea and vomiting, and constipation.

A chi-square test or Fisher test was used to analyze categorical or nominal variables (summarized as numbers and percentages). The Fischer exact test was used when at least one of the cells in the 2x2 contingency table had an expected frequency <5. Continuous variables were summarized as mean and standard deviation, for which an independent T-test and Mann-Whitney U test was used to analyze the results with the p-value ≤ 0.05 was taken as statistically significant. All statistical analysis was done using EPI INFO version 7.2.1.0 statistical software.

RESULTS AND DISCUSSION

The study was conducted on 60 patients. The two groups were comparable in terms of demographical data, duration of surgery, and time for extubation. There were no significant differences between 2 groups based on the age ($p = 0.947$), gender ($p = 0.789$), weight ($p = 0.892$), duration of surgery ($p= 0.289$), and time for extubation ($p = 0.279$) (Table 1).

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Table 1. Demographic Variables, Surgery, and Anaesthetic Data

Parameters	Group 1 Tramadol; (N = 30)	Group 2 Buprenorphine; (N = 30)	p-value
Age (Years) [mean ± SD]	47.6 ± 8.23	46.9 ± 8.31	0.947*
Gender Male Female	18 (60) 12 (40)	20 (66.7) 10 (33.3)	0.789**
Weight (kg) [mean ± SD]	58.1 ± 5.53	58.3 ± 5.78	0.892*
Duration of Surgery (min) [mean ± SD]	98.37 ± 12.64	101.53 ± 10.14	0.289*
Time for extubation (min) [mean ± SD]	123.17 ± 12.53	126.4 ± 10.28	0.279*

*Based on the independent T-test, significant if p-value ≤ 0.05
**Based on the chi-square rest, significant if p-value ≤ 0.05

The analysis of variance showed that VAS scores were initially higher in the buprenorphine group for the first 3 hours postoperatively (i.e., till 24 hours of applying the buprenorphine patch) but after that, the buprenorphine group consistently had lower pain scores throughout the study period (Figure 1).

We observed that patients of the buprenorphine group initially had higher pain scores than the tramadol group for the first 3 hours post-operatively but after that throughout the study period, the VAS was less in the buprenorphine group. This was so because though we applied the buprenorphine patch 18 hours before the start of the surgery but its analgesic effect started only 22-24 hours after application as has been seen in many previous studies (5,6), while subjects in the tramadol group received 100mg IV tramadol loading following skin closure so had better pain relief for the first 2-3 hours only but after the initial 3-4 hours post operatively, the VAS was less in the buprenorphine group throughout the study period, though 50mg tramadol was given 6 hourly.

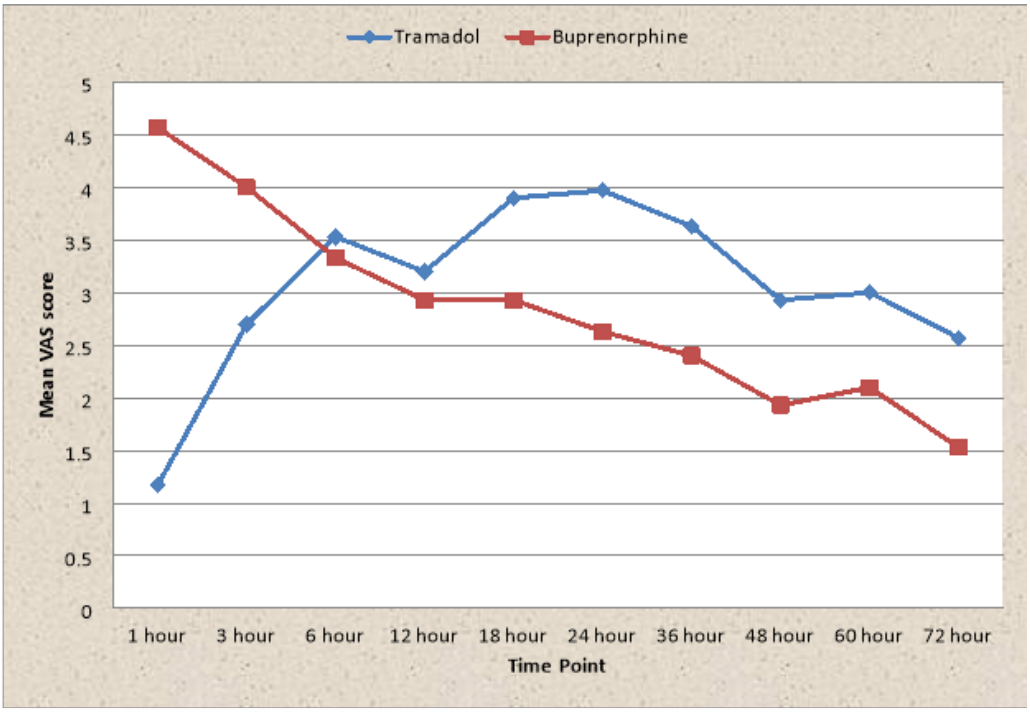

Figure 1. Postoperative Visual Analogue Score 0-10

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This may be because IV bolus drug administration may cause excessive therapeutic plasma concentration soon after administration, and later the drug levels drop to a subtherapeutic level causing pain while transdermal administration provides a steady state plasma concentration of the desired drug. However, as drug absorption from transdermal patch is delayed, it has to be applied preoperatively and use of it as a pre-emptive analgesic could lead to the development of adverse effects in the absence of painful stimuli in the preoperative period (2). Aortofemoral bypass surgery is a procedure utilized commonly for the treatment of aorto iliac occlusive disease. Patients with this disease often experience moderate to severe rest pain of the lower extremities and also need good postoperative pain management after aortofemoral bypass surgery. Thus, use of transdermal buprenorphine patches in these patients may be of great use. Also, these patients with peripheral vascular disease have an incidence of 37.9% associated renal dysfunction and buprenorphine which is metabolized in the liver has a potential safety in patients with renal dysfunction (7). No literature now is available about the use of transdermal buprenorphine patches in these aorto-occlusive disease patients.

Table 2. Comparison of Time to First Rescue Analgesic Given between the Both of Groups

Variable	Group 1 Tramadol (N = 30)	Group II Buprenorphine (N = 30)	p-value
Time to first rescue analgesia (hours) [mean ± SD]	14.46 ± 10.46	2.03 ± 1.9	< **0.001***

*Based on the independent T-test, significant if p ≤ 0.05

The first rescue analgesia requirement was earlier in the buprenorphine group (2.03 ± 1.9) hours than in the tramadol group (14.46 ± 10.46) hours. Based on the statistical test, there is a significant difference between Group I and Group II based on the time for first rescue analgesia with the p-value < 0.001 (Table 2).

However, with the passage of time, the buprenorphine group required a lower number of rescue analgesia than the tramadol group (Table 3). The buprenorphine group also received fewer rescue medicine (paracetamol) dose as compared to the tramadol group (Table 4).

Table 3. Comparison of Number of Rescue Analgesia at Different Time Intervals between Both the Study Group

Time Point	Group 1 Tramadol (N = 30)	Group 2 Buprenorphine (N = 30)	p-value
1 hour	1	22	< 0.001
3 hours	14	20	0.193
6 hours	16	9	0.116
12 hours	14	6	0.055
18 hours	19	5	< 0.001
24 hours	18	6	0.001
36 hours	18	5	0.001
48 hours	12	3	0.017
60 hours	10	3	0.060
72 hours	10	1	0.008

*Based on the Fischer exact test, significant if p ≤ 0.05

Table 4. Comparison of Paracetamol Dose Received between the Both of Groups

Variable	Group I Tramadol (N = 30)	Group II Buprenorphine (N = 30)	p-value
Dosage of paracetamol injection (gram) [mean ± SD]	4.2 ± 1.35	2.23 ± 0.84	0.001

*Based on the Mann-Whitney test, significant if p ≤ 0.05

Rescue analgesic doses accounted for a total of 132 in the tramadol group, out of which 126 doses were of Paracetamol (1 gram) and 6

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doses were of diclofenac (75 mg IM) while in the buprenorphine group total number of rescue analgesic doses was only 80, which included 67 doses of paracetamol and 13 doses of diclofenac ($p < 0.001$).

Desai et al., (8) observed that an average number of diclofenac tablets consumed in 7 postoperative days in transdermal buprenorphine (10 mg) patch group was 2.4 ± 2.2 and in oral tramadol (50 mg TID) group was 6.6 ± 3.0, and an average number of paracetamol tablets consumed in 7 postoperative days in transdermal buprenorphine group was 0.68 ± 2.2 and in oral tramadol group was 1.9 ± 3.7, subjects in buprenorphine group needed less rescue analgesic then in tramadol group similar to our study.

Table 5. Side effect profile between the both of groups

Side effects	Group I Tramadol (N = 30) [N (%)]	Group II Buprenorphine (N = 30) [N (%)]
Nausea or vomiting	6 (20)	1 (3.3)
Constipation	2 (6.7)	1 (3.3)
No side effect	22 (73.3)	28 (93.33)

The incidence of postoperative nausea and vomiting was significantly lower in the buprenorphine group (3.3%) compared to the tramadol group (20%). Respiratory depression was not noticed in any of the group. Skin rash was not reported in any patient of the buprenorphine group (Table 5).

Different modalities of pain management have been utilized for the management of postoperative pain which has their benefits and side effects. Buprenorphine is a partial agonist at mu receptors with low oral bioavailability, increased lipid solubility, and low molecular weight which offers sustained pain relief through transdermal delivery (9,10).

Tramadol is a centrally acting analgesic with weak opioid agonist properties and low dependence. Therefore, clinically relevant respiratory depression and abuse potential is not seen making it a suitable drug for use in post-operative analgesia (11,12). However. incidence of postoperative nausea and vomiting is quite high and it tends to accumulate in patients with renal failure. Therefore, it warrants caution in such high-risk patients (13). In the past a comparison has been done between transdermal buprenorphine and tramadol for non-cancer chronic pain in which buprenorphine has been found superior but only a few studies are there considering the use of transdermal buprenorphine for post-operative pain management (14). No study could be found of comparison of transdermal buprenorphine with IV tramadol for post-operative analgesia.

In this study, a transdermal buprenorphine patch of 10 mcg/hr was used for the management of post-operative pain in patients operated on aorto-iliac occlusive disease and compared with IV tramadol.

Desai et al., (8) compared transdermal buprenorphine 10mcg/h (which was applied 24 hours before surgery) with oral tramadol and observed that patients of the buprenorphine group had lower pain scores, less requirement of rescue analgesic and had decreased incidence of vomiting but VAS was more than 4 till 24 hours after surgery after which it started decreasing gradually lowest being 2.5 at 7th day. They concluded that transdermal Buprenorphine was more effective in decreasing post-operative pain after approximately 48 hours of applying the patch but in our study, the effect could be seen after 24 hours of the application of the Buprenorphine patch.

Prerana et al., (15) who studied a transdermal patch of Buprenorphine (20µg/hr),

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observed that patients belonging to the buprenorphine group were composed, comfortable, and easily roused throughout the study period, with mean sedation score being 1.93 ± 0.25. Z Arshad et al., (16) also concluded in their study that transdermal buprenorphine 10mcg/h is safe and efficacious for the management of post-operative pain.

We noted very few drug-related adverse effects in both the groups which were not statistically significant. The limitations of our study include the use of 10mcg/hr transdermal buprenorphine patch only for post operative pain management in patients with aortofemoral bypass surgery. Therefore, more studies are required to evaluate the efficacy of higher concentrations of buprenorphine transdermal patches in these surgeries.

CONCLUSION

Transdermal buprenorphine (10 microgram/hr) applied preoperatively is a safe and effective option for postoperative pain management in patients undergoing aortofemoral bypass surgery. It offers superior pain control, and reduces the need for rescue analgesia, thereby decreasing potential side effects as compared to intravenous tramadol.

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Conflict of Interest

None

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Authors' Contributions

All the authors were actively involved in study planning, study design, execution, writing of the articles, and arranging all the necessary materials required.

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Case Report

SURFACE ANATOMY-BASED CLAVIPECTORAL FASCIA PLANE BLOCK FOR CLAVICLE SURGERY

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ABSTRACT

Introduction: Clavicular fractures are often observed cases. In the majority of clavicle fractures, both in adults and children, the fracture is located in the midshaft. Generally, General Anesthesia techniques are usd in such instances, as regional anesthesia through peripheral nerve block often presents its own challenges. The clavipectoral fascial plane block was first introduced in 2017. Apart from its ease of implementation, the Surface Anatomy-Based Clavipectoral Plane Block can avoid the risks associated with other regional anesthesia techniques such as Plexus Brachialis Block or Interscalene Block. **Objective:** This report aims to provide an overview of the procedures for carrying out surface anatomy-based clavipectoral fascia plane block for clavicle surgery. **Case Report:** A 33-year-old man with the primary complaint of pain in the right shoulder following a fall while playing football. The patient was diagnosed with closed re-fracture of the clavicle (D) Allman Group I. Clavicle surgery was conducted with the Surface Anatomy-Based Clavipectoral Fascia Plane Block technique. In this patient, local anesthetic agents were administered as Levobupivacaine 0.375% in a volume of 20 cc. The operation lasts approximately 1.5 hours. The Patient's hemodynamic condition was stable during the surgery. The patient had no complaints and post-operative pain was effectively managed. **Conclusion:** The surface Anatomy-based Clavipectoral fascia plane block can be considered for clavicular surgery, especially in Allman Group type 1. Besides being easy to implement, this technique also poses fewer risks compared to other regional anesthesia techniques.

Keywords: Clavicula, Claviperctoral Fascia Plane Block, Clavicle Fractures, Fascia Clavipectoral, Traffic Accident and Injury

ABSTRAK

Pendahuluan: Fraktur pada tulang klavikula merupakan kasus yang umum ditemui. Pada sebagian besar fraktur klavikula, baik pada dewasa maupun anak-anak, lokasi patahan terletak pada bagian midshaft. Secara umum, teknik anestesi umum menjadi pilihan pada kasus-kasus seperti ini, karena teknik anestesi regional melalui *peripheral nerve block* seringkali memberikan tantangan tersendiri. *Clavipectoral fascial plane block* dikenalkan pertama kali pada tahun 2017, Selain karena kemudahan dalam pelaksanaannya, *Clavipectoral Plane Block* berbasis permukaan anatomis dapat menghindari resiko yang mungkin terjadi pada teknik regional anestesi lainnya seperti pada Blok Plexus Brachialis ataupun *Interscalene Block*. **Tujuan:** Laporan ini bertujuan untuk memberikan gambaran mengenai prosedur pelaksanaan blok bidang fascia clavipectoral berbasis anatomi untuk operasi pembedahan klavikula. **Laporan Kasus:** Seorang laki-laki usia 33 tahun dengan keluhan utama nyeri pada bahu kanan setelah terjatuh saat bermain sepak bola. Pasien didiagnosis dengan *closed re-fracture clavicula* (D) Allman Group I, dilakukan Tindakan ORIF Clavicula dengan teknik *Clavipectoral Fascia Plane Block* berbasis permukaan anatomis. Pada pasien ini digunakan agen anestesi lokal yaitu Levobupivakain 0.375% sebanyak 20 cc. Operasi berlangsung kurang lebih 1.5 jam. Kondisi hemodinamik pasien terbilang stabil selama operasi berlangsung. Pasien tidak memiliki keluhan sepanjang operasi dan nyeri pasca operasi dapat tertoleransi dengan baik. **Kesimpulan:** *Clavipectoral fascial plane block* berbasis permukaan anatomis dapat menjadi pilihan pada kasus pembedahan tulang klavikula terutama pada kelompok Allman 1. Disamping pelaksanaannya yang mudah, teknik ini juga memberikan risiko yang lebih sedikit jika dibandingkan teknik regional anestesi lainnya.

Kata kunci: Clavicula, *Claviperctoral Fascia Plane Block, Fraktur Clavicula, Fascia Clavipectoral*, Kecelakaan Lalu Lintas dan Cedera

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INTRODUCTION

Clavicular fractures are cases that we often encounter. A clavicle fracture can result from various causes, such as a traffic accident or a fall during activities. In the majority of clavicle fractures, both in adults and children, the fracture is located in the midshaft (1). Generally, the general anesthesia (GA) technique is preferred in such instances, as regional anesthesia through peripheral nerve block often presents its own challenges. Several published case reports and series have been reported the efficacy of a brachial plexus block (interscalene approach) or a combination block (interscalene with cervical superficialis) (2,3). However, performing two different blocks plus using ultrasonography as guidance can be something time-consuming.

The clavipectoral fascial plane block was first introduced in 2017 by Dr. Luis Valdes at the European Society of Regional Anesthesia and Pain Therapy Congress (4–7). Apart from its ease of implementation, the Surface Anatomy-Based Clavipectoral Plane Block can avoid the risks associated with interscalene blocks, including ipsilateral nerve palsy, vocal cord paralysis, and pneumothorax (3). Blocks can deliver effective post-operative analgesia when utilizing long-acting agents, less opioid use, and disminished postoperative nausea and vomiting in comparison to general anesthesia (8).

CASE REPORT

A 33-year-old man presented with complaints of pain in the right shoulder following a fall during playing soccer. The patient reported that he fell with his right shoulder hitting the field first. There was no history of fainting, vomiting, or seizures. Subsequent to the incident, the patient reported exacerbated pain in the right shoulder with movement. Previous history of asthma, allergies, hypertension, diabetes mellitus, seizures, breathing difficulties, and familial diseases are denied. The patient experienced a previous anesthesia procedure in 2007 for Clavicle Surgery and again in 2010 for the Removal of an Implant from the clavicle.

The physical examination found a height of 174 cm, a weight of 97 kg with a BMI of 32 kg/m^2 categorizing him as obese class I. The vital signs examination found a Blood Pressure of 110/70 mmHg, Heart Rate of 84 beats per minutes, Respiratory Rate of 20 breaths per minutes, temperature of 36.5°C, and oxygen saturation (SpO2) of 98% with nasal cannula of 3 lpm oxygen in a supine position. Airway is clear, respiration is sufficient, circulation is normal. The examination of heart and lung found no abnormalities.

Local examination of the right claviclular region found cicatricial changes, accompanied by swelling in the middle 1/3, unclear deformity. Tenderness present, crepitus observed in the middle 1/3 of the clavicle, neurovascular disturbance disruption absent, SpO2 digits 1-5: 97%-99%. The movement examination found limited shoulder range of motion (ROM), positive discomfort, but the elbow and wrist exhibited complete range of motion.

The results of PA Thoracic X-ray indicate lung contusion, mild bilateral pleural effusion with differential diagnosis of Hematothorax, a comminuted fracture in the middle 1/3 of the right clavicle accompanied by soft tissue swelling, and complete fractures of the right posterior ribs 3, 4, and 5. Assessment of invalid cast conducted (Figure 1).

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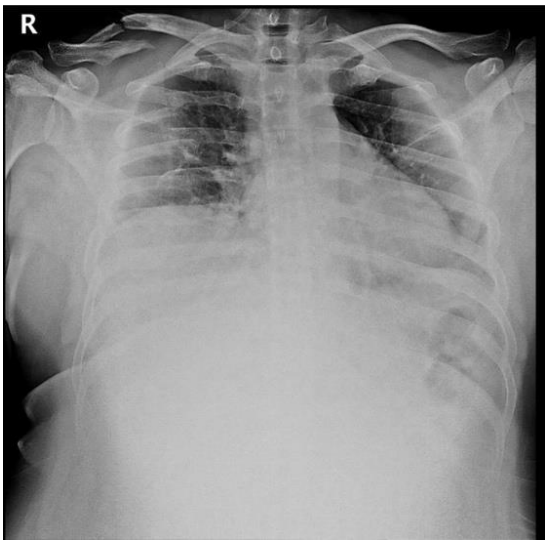

Figure 1. Posteroanterior Thoracic X-ray Before Surgery

Preoperative anesthetic assessment indicated a 33-year-old male with close re-fracture of the clavicle (D) Allman Group I, segmental type, scheduled for open reduction and internal fixation (ORIF) of the clavicle using an S-plate, with a physical status classified as ASA II, and a plan for Clavipectoral Block. The patients presented with lung contusions, mild bilateral pleural effusion, and Hematothorax, without severe respiratory distress. The patient's untritional state is indicated by a BMI of 32 kg/m2 (categorized as Obese Class I)

The patient was scheduled for clavicle surgery utilizing an S-plate, clasified as ASA II, with clavipectoral block anesthesia planned. The patient's operative preparation and management will be explained in detail before to, during, and after the operation. In this case, ORIF of the clavicle was performed utilizing the clavipectoral block anesthesia technique. In this patient, Levobupivacaine 0.375% was administered as 20 cc with injection in three sides of the clavicle. The injection was administered in the medial end, the location of the fracture, and the lateral end.

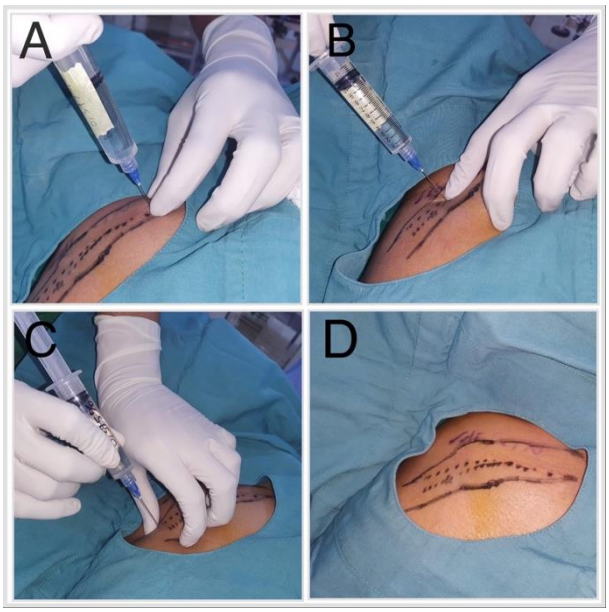

Figure 2. Injection Site of the Local Anesthetic Agent.
(A: Injection at the lateral end site; B: Injection at the fractured bone site; C: Injection at the medial end site; D: Clavicle and Incision marker from the surgeon)

The operation lasts approximately 1.5 hours. The hemodynamic stability of operation is maintained as,a systolic blood pressure of 110-140 mmHg anddiastolic blood pressure of 70-79 mmHg,respiratory rate of 18-20 breaths perminute,heart beart of 75-90 beats per minute, lifting strength, regular SpO2 of98% with nasal cannula at 3 lpm oxygen.

Table 1. Intraoperative Hemodynamic Monitoring

Hemodynamic	Value						
Time (WIB)	13.00	13.15	13.30	13.45	14.00	14.15	14.30
Systole (mmHg)	140	136	110	115	110	140	132
Diastole (mmHg)	79	74	70	72	74	76	74
HR (bpm)	90	88	70	72	76	83	88
SpO2 (%)	100	100	100	98	99	100	100

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The administered surgical medications include Ondansetron 4mg intravenously, Injection of Paracetamol 1 gr intravenously, and Midazolam 3 mg. Throughout the duration, 3 lpm of O_2 is administered via a nasal cannula.

Hemodynamics during surgery are presented in table 1. The postoperative condition was recorded with vital signs of blood pressure at 138/77 mmHg, heart rate at 82 beats per minute, respiratory rate at 20 breaths per minute, and oxygen saturation (SpO2) at 98% while receiving oxygen through nasal cannula at 3 liters per minute. Following the completion of the operation, the patient was transferred back to the ward. The patient was administered paracetamol 1 gram every 8 hours for postoperative pain treatment.

DISCUSSION

A frequently encounter case is clavicle surgery. Regional anesthesia options for the clavicle consist of plexus blocks, truncal blocks, or fascial plane blocks. Plexus blocks involve the cervical plexus (such as superficial cervical plexus block or selective supraclavicular nerve block) with or without brachial plexus block (such as interscalene block) (2,3,9). The clavipectoral fascial plane block was first introduced in 2017 by Dr. Luis Valdes at the European Society of Regional Anesthesia and Pain Therapy Congress. The CFPB can administer anesthetic or analgesia to the clavicle, overcoming the shortcomings of other blocks associated with plexus blocks (6). Although, the CFPB was initially administered with ultrasound guidance, can alternatively be performed using anatomical marker guidance with equal effectiveness. Apart from its convenience, the CFPB also provides through reduced risk relative to other block techniques (7,10). However, the CFPB also has weaknesses, particularly when the fracture is not centrally located on the clavicle or if the operator performs an incision sufficiently broad to pass through the clavicle.

However, effective planning and collaboration between the anesthesiologist and operator are needed to identify the area of operation to be carried out. This technique has limitations, especially regarding the operating area, so it is necessary to communicate comprehensively with the operator before action begins.

CONCLUSION

As time progresses, new regional anesthetic techniques are also developing which combine various perspectives, thereby enhancing our selection of anesthesia techniques. The clavipectoral block can be an option as a standalone anesthetic technique or used as part of multimodal analgesia. Despite its advantages, this technique also has weaknesses including limited types of operations that can be applied. The clavipectoral block technique can be considered for patients undergoing clavicular surgery, but it is risky when general anesthesia is administered without access to equipment resources such as ultrasound.

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Conflict of Interest

The authors declare no conflict of interest.

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Author's Contributions

All authors have contributed to all processes in this case report.

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Case Report

A DIAGNOSTIC CHALLENGE IN THE DIFFERENTIAL DIAGNOSIS OF RECURRENT SEIZURES DURING PREGNANCY: EPILEPSY VERSUS ECLAMPSIA

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ABSTRACT

Introduction: Seizures during pregnancy are associated with adverse outcomes for mothers and infants. Seizures during pregnancy can be associated with multiple factors. To establish effective treatment and management of seizures, it is important to identify all of the factors that may contribute to seizures during pregnancy. **Objective:** This study aimed to evaluate and identify the cause of seizures in pregnancy to facilitate appropriate treatment. **Case Report:** We present a case of a 32-week pregnant woman who experienced eclampsia and recurrent seizures during the peripartum period. The patient had a history of inadequately managed epilepsy. Seizure management required multiple medications, including magnesium sulfate, benzodiazepine, and phenytoin. The patient underwent an emergency caesarean utilizing the Rapid Sequence Intubation (RSI) procedure and general anesthesia to rescue the baby. Nicardipine, furosemide, isosorbide dinitrate, captopril, spironolactone, and hydrochlorothiazide were used to manage blood pressure. The patient needs to be continuously observed, and the therapy should be adjusted according to the patient's condition. **Discussion:** The patient had a history of epilepsy and had experienced two bouts of generalized seizures with characteristics of eclampsia before being arrived at the emergency room. Determining how to control the seizures in this spesific individual was a challenge. The primary therapy of patients with active seizures should include maintaining the airway, respiration, and circulation. The therapeutic objectives are immediate delivery of a viable fetus and maintenance of maternal health. Perioperative management aims to control blood pressure and seizures, maintain hemodynamics, manage anesthesia for terminating a pregnancy, and support critical care management for any potentially fatal complications from this condition. **Conclusion:** Seizures in pregnancy are attributable not just to eclampsia but can also cause by another or concurrently together with other causes. Early diagnosis and appropriate treatment are required to achieve the best outcome for this patient.

Keywords: Eclampsia, Epilepsy, Pregnancy, Seizure

ABSTRAK

Pendahuluan: Kejang selama kehamilan berkontribusi terhadap luaran ibu dan perinatal yang buruk. Kejang selama kehamilan dapat disebabkan oleh banyak faktor. Untuk menentukan pengobatan dan pengendalian kejang yang tepat, penting untuk mengidentifikasi semua faktor yang mungkin berkontribusi terhadap kejang selama kehamilan. **Tujuan**: Laporan kasus ini bertujuan untuk mengevaluasi dan mengidentifikasi penyebab kejang pada kehamilan untuk mendapatkan tatalaksana yang tepat. **Laporan Kasus**: Seorang wanita hamil 32 minggu mengalami eklamsia dan kejang berulang selama masa peripartum. Pasien mempunyai riwayat epilepsi yang tidak terkontrol sejak sebelum hamil. Pengendalian kejang pada pasien ini memerlukan beberapa obat termasuk magnesium sulfat, benzodiazepin, dan fenitoin. Pada pasien segara dilakukan operasi caesar darurat dengan anestesi umum. Induksi dilakukan dengan Teknik *Rapid Sequence Intubation* (RSI). Beberapa obat yang digunakan untuk mengendalikan tekanan darah diantaranya nicardipine, furosemide, isosorbide dinitrate, captopril, spironolactone, dan hydrochlorothiazide. Pasien memerlukan observasi lanjutan di ruang perawatan intensif (ICU) dan terapi disesuaikan dengan kondisi pasien. **Diskusi**: Pasien mengalami dua kali serangan kejang umum dengan karakteristik eklampsia sebelum tiba di Instalasi Gawat Darurat (IGD). Pasien memiliki riwayat epilepsi sebelumnya sehingga penentuan diagnosis dan tatalaksana pengendalian kejang pada pasien ini merupakan sebuah tantangan. Penatalaksanaan awal pasien dengan kejang aktif harus mencakup pemeliharaan jalan napas, pernapasan, dan sirkulasi. Terminasi kehamilan diperlukan untuk menyelamatkan ibu dan bayinya. Penatalaksanaan perioperatif pasien bertujuan untuk mengontrol tekanan darah dan kejang, menjaga status hemodinamik, tatalaksana anestesi untuk terminasi

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kehamilan, dan manajemen perawatan kritis untuk setiap komplikasi yang berpotensi fatal pada kondisi ini. **Kesimpulan**: Kejang pada kehamilan tidak hanya disebabkan oleh eklamsia saja tetapi dapat juga karena sebab lain atau bersamaan dengan sebab lainnya. Diagnosis dini dan pengobatan yang tepat diperlukan untuk mencapai hasil terbaik bagi pasien ini.

Kata Kunci: Eklampsia, Epilepsi, Kehamilan, Kejang

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INTRODUCTION

Neurological diseases might be directly associated with pre-eclampsia, and eclampsia or may be related to pre-existing conditions such as epilepsy, multiple sclerosis, myasthenia gravis, brain tumors, cardiac, metabolic, and neuropsychiatric conditions. These conditions may cause neurological disorders during pregnancy and the puerperium, exacerbated by the physiological changes occuring during this period (1,2). Identifying the causative factors is important for obtaining appropriate treatment and managing seizures. The most frequent cause of seizures in pregnant women during the pregnancy-puerperal cycle is eclampsia. Eclampsia is commonly defined as the new onset of generalized tonic-clonic seizures or coma in pregnancy or postpartum accompanied by signs or symptoms of preeclampsia (3). The incidence of preeclampsia varies from 0.51 - 38.4%, with prevalence rates in developing countries ranging from 1.8 – 18%, while the incidence rate in Indonesia estimated at approximately 3.8-8.5%. In Indonesia, the Maternal Mortality Rate (MMR) in 2019 reached 305 per 100,000 live births, with severe preeclampsia accounting for 26.47% (76.97 per 100,000 live births) (4). Regardless, in situations that are resistant and have no improvement with conventional treatment, other possible causes of convulsive crises must be investigated or excluded. Epilepsy is one of the most common causes of seizures during pregnancy. Seizure in pregnancy can cause by various factors other than epilepsy or eclampsia, such as cerebral hemorrage, cerebral infarction, drug and/or alcoholic withdrawal, hypoglycemia, hypertensive encephalopathy, intracranial neoplasm, infections, and electrolyte imbalance (5,6). This neurological condition has a lifetime incidence of 1.5% in developing countries and 0.6% in industrialized nations (7). It is estimated that 0.3–0.7% of pregnant women have epilepsy. Women who had seizures in the year before becoming pregnant need to have their epilepsy closely monitored (1). This case report aims to evaluate and identify the cause of seizure in pregnancy to facilitate appropriate treatment.

CASE REPORT

A 28-year-old multigravida was referred to our secondary care facility from a peripheral primary care clinic due to frequent seizures and hypertension. Her medical history indicates that she had suffered inadequately managed epilepsy for 14 years. She was diagnosed with a singleton pregnancy at 32 weeks of gestation, with a history of inadequate antenatal care. The patient's family reported that the patient experienced tonic-clonic movements lasting two to three minutes. She had no previous history of hypertension, nevertheless, she had a history of generalized seizures since 14-years-old and was not on medication. Upon the patient's convulsion at home, the midwife from the public health care facility administered an initial treatment of 4 grams of magnesium sulfate for 20 minutes, followed by a maintenance dose of 6 grams, and referred to the hospital. The glasgow coma

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scale (GCS) at admission was 8 (E2M3V3), blood pressure (BP) measured 176/125 mmHg, heart rate (HR) was 150 bpm, respiratory rate (RR) was 20 times/minute, and temperature was 36.6°C. Laboratory tests at admission showed proteinuria (urine protein 3+) as detailed in table 1 and urine analysis in table 2. In the ER, the patient received magnesium sulfate 1 gram per hour, oxygenated with a non-rebreathing mask of 10 liters per minute, and underwent emergency cesarean section.

The patient was subsequently moved to the surgery room. Before surgery, the patient's condition was unstable. Basic monitoring was performed, which included pulse oximetry, heart rate, electrocardiography, and blood pressure assessment. The initial vital signs were: blood pressure of 171/101 mmHg, heart rate of 113 beats/min, respiratory rate of 29 times/minute in a semi-fowler position, and SpO2 of 98-99% with 10 liters/minute non-rebreathing mask oxygenation. Following preoxygenation, anesthesia was induced with Rapid Sequence Intubation (RSI), comprising midazolam 2 mg, fentanyl 50 mcg, propofol 100 mg, and rocuronium 40 mg, accompanied with cricoid pressure. The trachea was intubated using a cuffed orotracheal tube (7-mm internal diameter). Anaesthesia was maintained with 0.5-1% isoflurane in oxygen at a flow rate of 3 liters/minute. Hydration was maintained with a peripheral intravenous line (Ringer's lactate). The neonate had an Apgar score of 3 at birth. The Apgar score increased to 4 at 3 minutes and 5 at 5 minutes. The neonate was transferred to the neonatal intensive care unit (NICU) for further management under the pediatric supervision. The remaining intraoperative procedures were successfully performed. After completion of the surgery, she was transferred to the intensive care unit (ICU) for observation.

Table 1. Laboratory examination

Examination	Result
Haemoglobin	13.8 gr/dl
Leucocyte	15,200
Hematocrit	40.3%
Platelet	407,000
ALT	31.07 U/L
AST	11.22 U/L
Sodium	134.14 mmol/L
Potassium	4.02 mmol/L
Chloride	95.53 mmol/L
Calcium	0.92 mmol/L
Creatinine	1.27 mg/dl
Ureum	23.97 mg/dl
Bleeding time	2 minutes
Clothing time	9 minutes

Table 2. Urine analysis

Examination	Result
Spesific gravity	1.020
pH	6.0
Urine color	Cloudy yellow
Urine bilirubin	Negative
Urine protein	+++ (3+)
Urine glucose	Negative
Urine ketone	Negative
Blood	+++ (3+)

Following an emergency caesarean section, the patient was moved to the ICU for close monitoring. The patient was treated with continuous magnesium sulfate infusion, analgesia, and a furosemide pump to manage her blood pressure according to the hospital procedure. She was provided with a mechanical ventilator for her respiratory support. Within the next 30 minutes, her blood pressure suddenly increased to 239/136 mmHg. She received a continuous infusion of furosemide and isosorbide dinitrate (ISDN), an additional 25 mg of captopril, hydrochlorothiazide, and spironolactone to manage her blood pressure with an initial target to reduce her systolic blood pressure (SBP) to 160 mmHg and diastolic blood pressure (DBP) to 105 mmHg

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immediately. Nevertheless, it was challenging to regulate her blood pressure. Thus, treatment with titrated nicardipine infusion was administered. During her blood pressure spike, the patient experienced 3 episodes of seizures. She received 2 grams of intravenous magnesium sulfate, followed by continuous infusion of 1 gram per hour and 5 milligrams midazolam intravenously for every seizure episode. However, the seizure continues to persist despite having her blood pressure decreased to 140/83 mmHg (Figure 1).

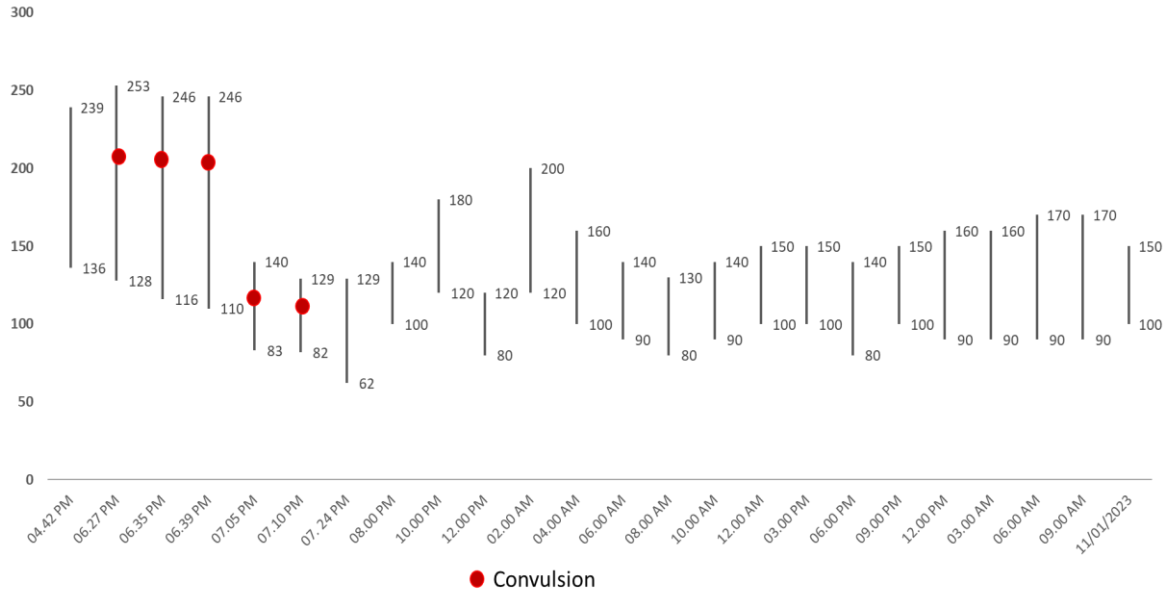

Figure 1. Blood Pressure and Seizure Monitoring

After achieving her blood pressure target, the patient experienced two more episodes of seizure, therefore we presume that the seizure was not purely caused by eclampsia. A loading dosage of phenytoin was administered to manage her seizures. Fortunately, following the injection of phenytoin, her seizures stopped and did not reoccur (Table 3).

The following day, the patient's vital signs were stable, as follows: blood pressure of 156/104 mmHg, heart rate of 103 beats/minutes, respiratory rate of 20 times/minutes, SpO2 of 98%, and a GCS ofE4VxM6, thus she was weaned off the ventilator and extubated. Blood pressure management was tapered off as shown in figure 1. The patient was moved to the regular ward on the same day. Upon follow-up the next day, the seizure did not reoccur and the vital signs were stable, then she was scheduled to have an electroencephalogram (EEG) test. The EEG test indicated that no epileptogenic wave was detected (Figure 1). We evaluated the patient's hemodynamic and clinical condition daily until stability was achieved with oral medication. The patient was hemodynamically and clinically stable, then she was discharged home. Her last medications included amlodipine, spironolactone, hydrochlorothiazide, cefadroxil, mefenamic acid, phenytoin, iron tablet, pyridoxine, and folic acid. The patient was advised to regularly consult with an obstetrician, cardiologist, and neurologist.

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Table 3. Blood Pressure and Seizure Management

Date	Time	Systolic	Diastolic	Note
1 August 2023	04.42 pm	239	136	Furosemide pump 10mg/h, ISDN pump 0.5 mg/h, captopril 25 mg, lisinopril 10 mg, amlodipine 10 mg, HCT 25 mg, spironolactone 25 mg.
	6.27 pm	253	128	MgSO4 2 gr bolus, MgSO4 drip 1 gr/h, midazolam 5 mg
	6.35 pm	246	116	MgSO4 2 gr bolus, MgSO4 drip 1 gr/h, midazolam 5 mg
	6.39 pm	246	110	MgSO4 2 gr bolus, MgSO4 drip 1 gr/h, midazolam 5 mg, nicardipin 1mcg/kg/min
	7.05	140	83	MgSO4 2 gr bolus, MgSO4 drip 1 gr/h, midazolam 5 mg, nicardipin drip stop
	7.10	129	82	MgSO4 2 gr bolus, MgSO4 drip 1 gr/h, midazolam 5 mg, phenytoin 15 mg/kg, phenytoin 3x1 amp
	7.24	129	62	MgSO4 1gr/hr, ISDN drip stop

DISCUSSION

Seizure disorder during pregnancy impact both maternal and perinatal complications. Apart from the idiopathic cause, other factors can induce seizures in pregnancy, such as eclampsia, antiphospholipid syndrome, cerebral infarction, drug and alcohol withdrawal, and hypoglycemia (5). Seizures during pregnancy frequently indicate symptoms of epilepsy or eclampsia. Seizure disorders associated with pregnancy are estimated to affect 0.3% to 0.5% of all pregnancies. Seizures occur during pregnancy are typically diagnosed as eclampsia. Eclampsia is defined by the occurrence of tonic-clonic, focal, or multifocal seizures that occur suddenly and are not attributeable from any underlying medical disorders. Eclampsia typically presents 48 hours after birth and after 20 weeks of gestation (6,8). The prevalence of eclampsia in the Western countries is estimated to be between 1 in 2000 and 1 in 3000 births; however, in developing nations with inadequate prenatal care, the incidence is 10 times greater (9). Eclamptic seizures generally subside within three to four minutes. The majority of patients exhibit a response in 10 to 20 minutes on average (10). Another frequent neurological condition that can arise during pregnancy is epilepsy. In India, over 2.5 million women are diagnosed with epilepsy, with up to 25% of them are within the reproductive age range. In Indonesia, regarding the prevalence of epilepsy during pregnancy, precise statistics are unavailable (6). Although most cases are uncomplicated, there are elevated obstetric risks and more deprived newborn outcomes compared to the general population. The frequency of seizures is increased during pregnancy in one-third of women with epilepsy (6,11). Our patient received inadequate antenatal care, and did not monitor her pregnancy, resulting in an unrecorded medical history during pregnancy, including hypertension. The patient came to the emergency room (ER) with two episodes of generalized seizure with characteristics of eclampsia accompanied by a history of epilepsy. Establishing effective seizures management for this spesific individual was a challenge.

Eclampsia is considered as one of the most severe acute pregnancy illnessesdue to its significant maternal and neonatal morbidity. The pathogenesis of eclamptic seizures remains uncertain. The theory for eclampsia involves alterations to autoregulation in the cerebral circulation, similar to hypertensive encephalopathy, as the blood-brain barrier

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(BBB) is disrupted and fluid, ions, and plasma proteins are able through the brain parenchyma (12). Epileptic seizures may manifest during the prepartum, intrapartum, or postpartum phases. Preeclampsia and eclampsia were presumed to manifest within 48 hours postpartum. Recent studies indicate that late or delayed postpartum eclampsia may occur more than 48 hours but less than 6 weeks after birth.

Pregnancy may cause the worsening of epilepsy. Deterioration during pregnancy may result a variety of factors, including poor compliance, nausea and vomiting, increased volume of distribution, changes in protein binding, increased drug clearance, lack of sleep, decreased absorption of antiepileptic medications from the gastrointestinal tract, hyperventilation during labor, and hormonal fluctuations. Pregnancy is associated with changes in metabolic hormones. Hormones such as progesterone and estrogen might affect the likelihood of seizures during pregnancy. The decrease of blood estrogen levels during pregnancy enhance the activity of the glutamate decarboxylase enzyme, hence diminishing the brain's production of gamma aminobutyric acid (GABA). A reduction in GABA levels in the brain will trigger an epileptic seizure. The physiologic alteration during pregnancy will cause hemodilution. Hormones such as progesterone and estrogen may influence the occurrence of seizures during pregnancy. The lowering of blood estrogen levels during pregnancy enhances the activity of the glutamate decarboxylase enzyme to become more active, which in turn reduces the brain's production of gamma amino butyric acid (GABA). The decrease in GABA levels in the brain will induce an epileptic seizure. Edema and fluid retention may result from diminished glomerular filtration. The hyponatremia develops from the fluid retention. This condition may cause seizures, increade neuronal excitability, and a partial disruption of the sodium pump (4,11,13).

Prolonged seizures exceeding five minutes, or multiple seizures within a five-minute interval without regaining consciousness, are deemed abnormal and carry a considerable risk of developing convulsive status epilepticus, a potentially life-threatening medical emergency that affects approximately 1% of pregnancies in women with epilepsy. Multiple assessments are available diagnosing epilepsy, including the history and neurological examination, neuroimaging with CT-scan and MRI, metabolic and genetic evaluation through the laboratory assay, and EEG, the most common prevalent test that is completely safe and relatively cost-effective (14). An EEG was conducted on our patient and the result indicates the absence of any epileptogenic. This condition can occur because the EEG captures brain activity solely during the testing period. Over 40% of individuals with epileptic conditions may exhibit a normal EEG. While identifying the cause of a brief loss of consciousness or other paroxysmal events clinically suggestive of epilepsy, epileptiform activity exhibits specificity but lacks sensitivity, as EEG sensitivity in epilepsy is relatively low, ranging from 25–56%, with better specificity, but again varying between 78–98%. Imaging is essential for obtaining a better understanding of the pathophysiology of eclampsia. In clinical practice, there should be additional restrictions on the decision to do CT or MR imaging as the first option to exclude hemorrhagic lesions or other serious consequences. Patients who have spesific neurological deficit, evidence of a mass effect, or a reduction in awareness should have CT or MR imaging. Up to 80–90% of women with eclampsia show abnormal neuroimaging results. Most common lesions are located in parieto-occipital lobes in the distribution of posterior

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cerebral arteries. This lesion results from endothelial damage-induced vasogenic oedema, along with other damages that contribute to the pathophysiology of eclampsia. A complex picture of cerebral pathology accompanied by pericapillary hemorrhages, cortical petechiae, cerebral oedema, and microinfarcts, can cause headaches, disorientation, seizures, and visual abnormalities (15). As illustrated by our patient's diminished level of consciousness, CT or MR imaging could be conducted to exclude other reasons or problems; however, due to facility limitations, CT imaging is not a feasible option.

The initial management of a pregnant patient experiencing an active seizure must prioritize the patient's airway, adequate respiration, and appropriate perfusion support. The goals of therapy include maintaining the mother's health, ensuring the immediate delivery of a viable fetus, and providing close attention to the fetus. The anesthetic approach utilized for patients with pre-eclampsia and eclampsia depends on various factors, including the method of delivery (vaginal or cesarean surgery), the patient's medical condition (coagulopathy, respiratory problems), and the patient's level of consciousness. In mild or moderate pre-eclampsia cases, the patient may be allowed to undergo with normal vaginal delivery. In severe pre-eclampsia or eclampsia cases, the patient must deliver the baby immediately.

Regional and general anesthesia may be considered as the anesthesia management for caesarean section. Regional anesthesia may be administered if the patient is conscious, seizure free, has stable vital signs, and has no symptoms of elevated intracranial pressure (ICP). In cases when a patient is unconscious due to factors such as eclampsia or post-ictal state, or when there are other complications including impending eclampsia, significant coagulation abnormalities, anatomical issues with regional block insertion, or infection at regional block site, general anaesthesia (GA) is preferred (16,17). Given that the patient in this case was unconscious and in required an emergency caesarean section, we chose to perform GA utilizing the RSI (Rapid Sequence Induction) approach. RSI is a technique that is used when rapid airway control is required as a precaution for patients who may be at risk of reflux and aspiration of gastric contents. RSI is almost often used in critical situations including unfasted patients or uncertain fasting status, as well as in cases involving trauma, emergency surgeries, resuscitation situations, and patients with diminished consciousness levels (18,19).

Women with eclampsia should be closely monitored for at least 72 hours (12). Magnesium sulfate is used to prevent recurrent convulsions in women with eclampsia. Maintenance infusion of 1–2 g/hour is advised after administering a loading dose either 4 or 6 grams over a duration of 20–30 minutes. Magnesium sulphate infusion should begin before surgery, and continue during the procedure as well as for 24 hours postoperatively (8). However, despite the administration of a maintenance infusion of magnesium sulfate, the patient experienced a recurrence 2 hours after birth. To manage repeated seizures, the patient received a 2 g intravenous (IV) magnesium sulfate bolus, which may be administered throughout 3 to 5 minutes. The patient's creatinine level is higher than 1.2 mg/dL, a maintenance dosage of 1 g/h should be administered after the loading dose of magnesium sulfate (20). However, the necessity of mechanical ventilation for the patient may induce anxiety, agitation, and restlessness might compromise hemodynamic stability. Consequently, the use of midazolam is reasonable in our patients. Midazolam is a

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fast-acting benzodiazepine utilized for sedation and as an anticonvulsant, including eclampsia (21). Midazolam is a benzodiazepine that is currently the recommended first-line drug for treating seizure and status epilepticus. If a patient does not respond to magnesium sulfate (20 minutes after the bolus or more than two recurrences), a health care professional may administer phenytoin (1,250 mg IV at a rate of 50 mg/minute), thiopental, or sodium amobarbital (250 mg IV in 3 minutes) (8).

The global prevalence of hypertension during pregnancy is 5%–10%. A hypertensive emergency is characterized between acute hypertension-mediated organ damage (HMOD) and significantly increased blood pressure. Labetalol or nicardipine, along with magnesium sulfate, is the first-line therapy for hypertensive crises in eclampsia. The initial target in the management of hypertensive emergencies in eclampsia is to decrease the blood pressure to a systolic blood pressure less than 160 mmHg and a disatolic blood pressure less than 105 mmHg. During the blood pressure spike following delivery, the patient received furosemide and isosorbide dinitrate (ISDN) continuous infusion, captopril, hydrochlorothiazide, spironolactone, and nicardipine continuous infusion to reach her blood pressure target immediately. However, despite achieving her blood pressure target, the patient had two more episodes of seizure, therefore we presume that the seizure was not solely attributeable to eclampsia. Epilepsy may contribute to the occurrence of seizures in our patients (22).

Most pregnant woman with epilepsy has a greater risk of complications due to seizures. Complications of pregnancy and labor for mothers with epilepsy significantly increase. Pregnant women with epilepsy had a higher incidence of hemorrhage during pregnancy, pre-eclampsia, labor induction, low birth weight (under 2,500 grams), low Apgar scores (less than 5 after one minute and less than 7 after five minutes), and neonatal mortality (7). Additionally, infant asphyxia happened to mothers who had epilepsy. Sixty percent of infants with low 1-minute Apgar scores developed asphyxia as did 40% of infants with low 5-min Apgar scores. Asphyxia of the infants indicates their potential vulnerability to the adverse effects of anticonvulsant medication. Pediatricians should notify physicians about this risk and provide their assistance. As illustrated by our patient, who had a low Apgar score after birth and an Apgar score of 3, the infant had severe hypoxia and recovered with appropriate resuscitation; nonetheless, the Apgar score remained low and showed severe asphyxia even after resuscitation. Following resuscitation, the infant was transferred to the neonatal intensive care unit (NICU) for continued treatment under medical supervision.

Perinatal asphyxia refers to the inadequate blood flow or gas exchange to or from the fetus during the antepartum, intrapartum, or postpartum periods, potentially resulting in increasing hypoxemia and hypercapnia. Generalized tonic-clonic seizures are detrimental to the developing fetus because of the elevated blood pressure, altered electrolyte levels, and oxygenation during a seizure. During a seizure, an increase in intrauterine pressure also lowers the flow of blood to the uterus. This leads to changes in the blood gas composition within the umbilical artery. Metabolic changes associated with prolonged generalized tonic-clonic seizures may result in fetal harm. Prolonge generalized tonic-clonic seizures can induce fetal bradycardia and could result in fetal demise, even without maternal hypoxia. Furthermore, the American College of Obstetricians and Gynaecologists states that it includes clinical

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conditions such as severe hypoxia and metabolic acidosis.

Acute asphyxia is also possible without leading to any pathological complications. However, a fetus that suffers from acute hypoxia may have metabolic acidosis, characterized by an increase in acid accumulation, and a decrease in tissue oxygenation. Asphyxia may also occur temporarily without resulting any pathological complications. Severe hypoxia in fetus may result in metabolic acidosis, acid accumulation, and a decrease in tissue oxygenation (23).

The limitation of this study since this is a single case report study, making our findings difficult to generalize to the broader population. The recommendation for further studies to arrange case series or cohort retrospective design with larger samples is still needed to confirm these findings.

CONCLUSION

Seizure disorders during pregnancy are associated to an increased risk of negative outcomes for mothers and newborns. A recent study indicates that pregnant seizures are not usually caused by eclampsia. It is important to distinguish atypical symptoms from other reasons, such as epilepsy, when the clinical condition worsens. A better outcome is mainly based on a multidisciplinary approach that includes early diagnosis along with an appropriate therapeutic strategy.

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Conflict of Interest

The author(s) claimed that they had no possible conflicts of interest, regarding the case report, the text, and the publication of this paper.

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Authors' Contributions

All authors contributed significantly in writing this case report.

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Case Report

ACUTE LUNG OEDEMA IN SEVERE PRE-ECLAMPSIA: ADVANCED MANAGEMENT AND ANESTHETIC INTERVENTIONS

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ABSTRACT

Introduction: Acute Lung Oedema (ALO) during pregnancy is an uncommon but potentially life-threatening condition, particularly when associated with severe pre-eclampsia. This critical obstetric emergency requires prompt recognition and comprehensive management to prevent adverse maternal and fetal outcomes. **Objective:** This report aims to highlights the management of a complex case of ALO in a pregnant patient with severe pre-eclampsia, underscoring the essential role of multidisciplinary collaboration, evidence-based protocols, and individualized care in achieving favorable outcomes. **Case Report:** A 30-year-old woman at 29–30 weeks gestation presented with significantly reduced consciousness and severe shortness of breath. Clinical examination revealed hypertension, tachycardia, and profound hypoxemia, with radiological evidence of pulmonary oedema. The diagnosis included severe-feature pre-eclampsia complicated by acute respiratory distress syndrome (ARDS) secondary to ALO. Endotracheal intubation was used to protect the mother's airway, mechanical ventilation was used to help her get enough oxygen, and her blood pressure and heart rate were stabilized right away. Fluid therapy was carefully monitored to avoid exacerbating pulmonary oedema. Obstetric management prioritized delaying delivery until maternal stabilization was achieved. A surgical intervention under general anesthesia resulted in the delivery of a moderately distressed neonate. Postoperative care in the intensive care unit included continued mechanical ventilation, sedation, and meticulous fluid management. Gradual stabilization allowed for successful weaning off ventilatory support, extubation, and transfer to a general hospital ward. **Discussion:** Management strategies were guided by the ABCDE principle, targeting reductions in left ventricular preload and afterload, adequate oxygenation, and infection prevention. The case emphasizes the value of early diagnosis, prompt intervention, and interdisciplinary collaboration involving obstetricians, intensivists, and anesthetists. **Conclusion:** This case illustrates the importance of early recognition, swift intervention, and tailored care in managing ALO associated with severe pre-eclampsia. Comprehensive, team-based approaches are critical for optimizing maternal and neonatal outcomes in such high-risk scenarios.

Keywords: Acute Lung Oedema, Acute Respiratory Distress Syndrome, Intensive Care Unit, Obstetric Intensive Care, Severe Pre-eclampsia

ABSTRAK

Pendahuluan: Edema Paru Akut (ALO) selama kehamilan merupakan kondisi yang jarang terjadi namun berpotensi mengancam jiwa, terutama jika dikaitkan dengan pre-eklampsia berat. Kegawatdaruratan obstetri yang kritis ini membutuhkan pengenalan yang cepat dan manajemen yang komprehensif untuk mencegah hasil yang merugikan bagi ibu dan janin. **Tujuan:** Laporan ini bertujuan untuk menyoroti manajemen kasus ALO yang kompleks pada pasien hamil dengan preeklampsia berat, menggarisbawahi peran penting kolaborasi multidisiplin, protokol berbasis bukti, dan perawatan individual dalam mencapai hasil yang baik. **Laporan Kasus:** Seorang wanita berusia 30 tahun dengan usia kehamilan 29-30 minggu datang dengan penurunan kesadaran dan sesak napas yang parah. Pemeriksaan klinis menunjukkan adanya hipertensi, takikardia, dan hipoksemia berat, dengan bukti radiologis adanya edema paru. Pasien di diagnosis dengan pre-eklampsia berat dengan Sindrom Gangguan Pernafasan Akut (ARDS) yang disebabkan oleh ALO. Penanganan segera dilakukan dengan intubasi endotrakeal untuk perlindungan jalan napas, ventilasi mekanis untuk mendukung oksigenasi, dan intervensi untuk menstabilkan hemodinamik ibu. Terapi cairan dipantau dengan hati-hati untuk menghindari memperburuk edema paru. Manajemen kebidanan diprioritaskan untuk menunda persalinan sampai stabilisasi ibu tercapai. Intervensi bedah dengan anestesi umum menyebabkan kelahiran neonatus dengan gawat janin sedang.

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Perawatan pasca operasi di ruang perawatan intensif termasuk ventilasi mekanis yang berkelanjutan, sedasi, dan manajemen cairan yang cermat. Stabilisasi bertahap memungkinkan penyapihan dukungan ventilasi, ekstubasi, dan pemindahan ke bangsal rawatan biasa. **Diskusi:** Strategi penatalaksanaan dipandu oleh prinsip ABCDE, yang menargetkan pengurangan preload dan afterload ventrikel kiri, oksigenasi yang memadai, dan pencegahan infeksi. Kasus ini menekankan pentingnya diagnosis dini, intervensi yang cepat, dan kolaborasi interdisipliner yang melibatkan dokter kandungan, dokter intensif, dan dokter anestesi. **Kesimpulan:** Kasus ini menggambarkan pentingnya pengenalan dini, intervensi cepat, dan perawatan yang disesuaikan dalam menangani ALO yang terkait dengan preeklampsia berat. Pendekatan komprehensif berbasis tim sangat penting untuk mengoptimalkan hasil maternal dan neonatal dalam skenario berisiko tinggi seperti ini.

Kata kunci: Edema Paru Akut, Perawatan Intensif Kebidanan, Preeklampsia Berat, Sindrom Kesulitan Pernapasan Akut, Unit Perawatan Intensif

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INTRODUCTION

Acute lung oedema (ALO) in pregnancy is a rare but life-threatening condition with high maternal and perinatal morbidity and mortality and is one of the complications of pre-eclampsia with an incidence ranging from 0.08% to 1.5% (1,2) The definitive treatment for pre-eclampsia is delivery (3). We report a case of severe pre-eclampsia complicated by pulmonary edema, in which delivery was delayed for maternal stabilization before a caesarean section under general anesthesia was performed.

The objective of this case report is to discuss the management of ALO in pregnancy complicated by severe pre-eclampsia, highlighting how important it is to use evidence-based multidisciplinary approaches to improve outcomes for both the mother and the baby.

CASE REPORT

A 30-year-old pregnant female with a decrease in consciousness for the past hour was referred to the anesthesiology department due to termination of pregnancy. The patient complained of severe shortness of breath, followed by a gradual decline in consciousness, and was unresponsive when examined. The patient was on her 7th pregnancy of 29–30 gestational weeks, had a bad obstetric history due to 5 abortions, and had no children. The fetal movement was within normal limits with a fetal heart rate of 158 bpm. The patient had a history of hypertension for the past week and has been taking methyldopa 3 x 500 mg and nifedipine 3 x 10 mg. History of other problems was denied.

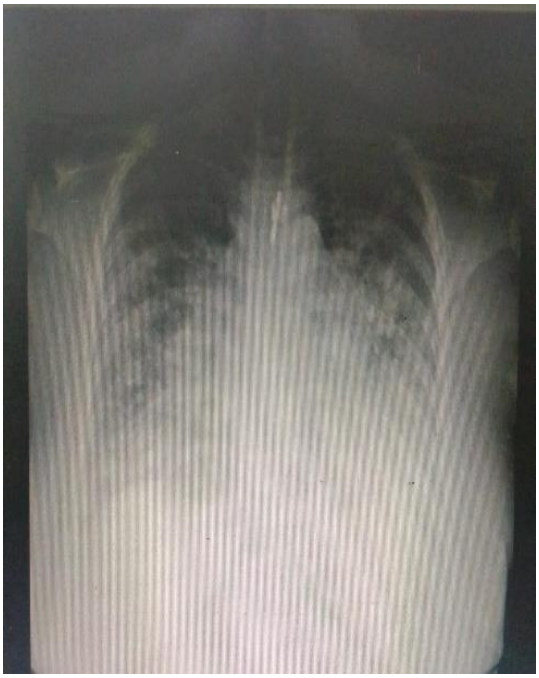

Figure 1. Chest X-ray

The physical examination revealed consciousness was stupor (GCS E1M2V1), blood pressure was 175/111 mmHg, heart rate was 156 bpm, respiratory rate was 36 bpm,

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SpO2 was 63% with NRM 15 lpm. Body mass index was 29.77 kg/m^2 (overweight), with vesicular breathing sounds accompanied by crackles in both lungs and dullness to percussion of the lungs. The laboratory result was within normal limit with hemoglobin 9.8 g/dL, and urine protein +1. The thoracic x-ray revealed cardiomegaly with pulmonary oedema. The blood gas analysis showed pH was 6.97, pCO_2 was 109.7 mmHg, pO2 was 70 mmHg, HCO3 was 25.4 mmol/L, BE was -6, SO_2C was 80%, and lactate was 4.60 mmol/L.

The diagnosis was G7P1A5, gravida 29 – 30 weeks with severe feature pre-eclampsia, and acute respiratory distress syndrome (ARDS) due to ALO. Early management was endotracheal intubation with ETT No. 7.0, oxygenation, transport of the patient to the ICU, and ventilator mode AC PC Pi 19 RR 16 PEEP 8 FiO2 100% for the first hour and then tapering of the FiO2. The patient was in head-up position of 30˚, given IVFD Ringer lactate 20 cc/hr, fentanyl 10 mcg/hr, propofol 100 mg/hr, rocuronium 20 mg/hr, omeprazole 2 x 40 mg IV, furosemide 40 mg IV loading dose followed by 5 mg/hr IV, nebulized combivent and Pulmicort / 8 hr.

In the next 8 hours, the patient's blood pressure was 125/87 mmHg, HR 105 bpm, RR 16 bpm, peripheral saturation was 98 % (AC PC Pi 19 RR 16 PEEP 8 FiO2 60%). The P/F ratio was 245. The blood gas analysis showed pH 7.33, pCO2 39.2 mmHg, pO2 147 mmHg, HCO3 22 mmol/L, BE was -5, and SaO2 99%. Urine output was 2.63 cc/kg/hr, with a balance was (-) 1558 cc. We tried to wean off the ventilator and sedation drugs. Four hours later, the patient's consciousness was E4M6Vett, blood pressure 137/94 was mmHg, HR was 95 bpm, RR was 22 bpm, SpO2 was 98% (SIMV PC Pi 19 RR 10 PS 12 PEEP 8 FiO2 40%). Echocardiography showed EF 49%, global normocinetic, valve within normal limits, TAPSE 20, and IVC 18. We planned to terminate the pregnancy.

Sectio Caesarea was performed under general anesthesia, induction with propofol 100mg, fentanyl 100 mcg, and relaxant using rocuronium 20 mg, all intravenously. The procedure lasted approximately 2 hours and the baby was born with an APGAR SCORE of 4/6 with a birth weight of 1100 grams. Postoperatively the patient was sedated in the ICU with ETT retention. Breathing was fully controlled with a ventilator until 6 hours postoperatively with ventilator mode AC VC Pi 18 RR 14 PEEP 8 FiO2 50%. Furosemide still administered of 5 mg/hour with six hours postoperatively, the ventilator and sedation were weaned. The patient was fully conscious and extubated one day postoperatively.

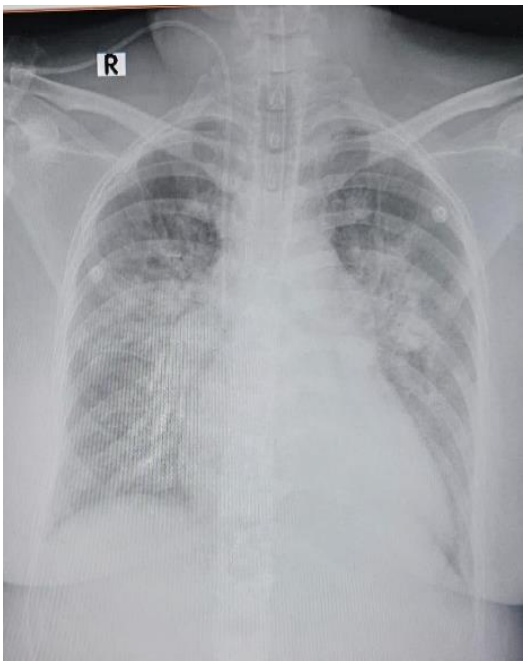

Figure 2. Chest X-ray Post Intubation

DISCUSSION

Pulmonary edema is defined as the abnormal accumulation of extravascular fluid in the lung parenchyma (4,5). Pulmonary edema can be characterized as either cardiogenic or non-cardiogenic. Pregnancy

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causes physiological changes that increase the risk of developing pulmonary edema (5,6). ALO in pregnant women is an uncommon yet life-threatening occurrence. The incidence varies between 0.08% and 3% (7).

During a normal pregnancy, both pulmonary and systemic vascular resistance drop dramatically. The gradient between colloid osmotic pressure and pulmonary capillary wedge pressure lowered by around 30%, increasing the susceptibility of pregnant women pulmonary oedema. Pulmonary oedema is caused by either an increase in cardiac preload (such as fluid infusion) or increased pulmonary capillary permeability (such as in pre-eclampsia), or both (6,8,9).

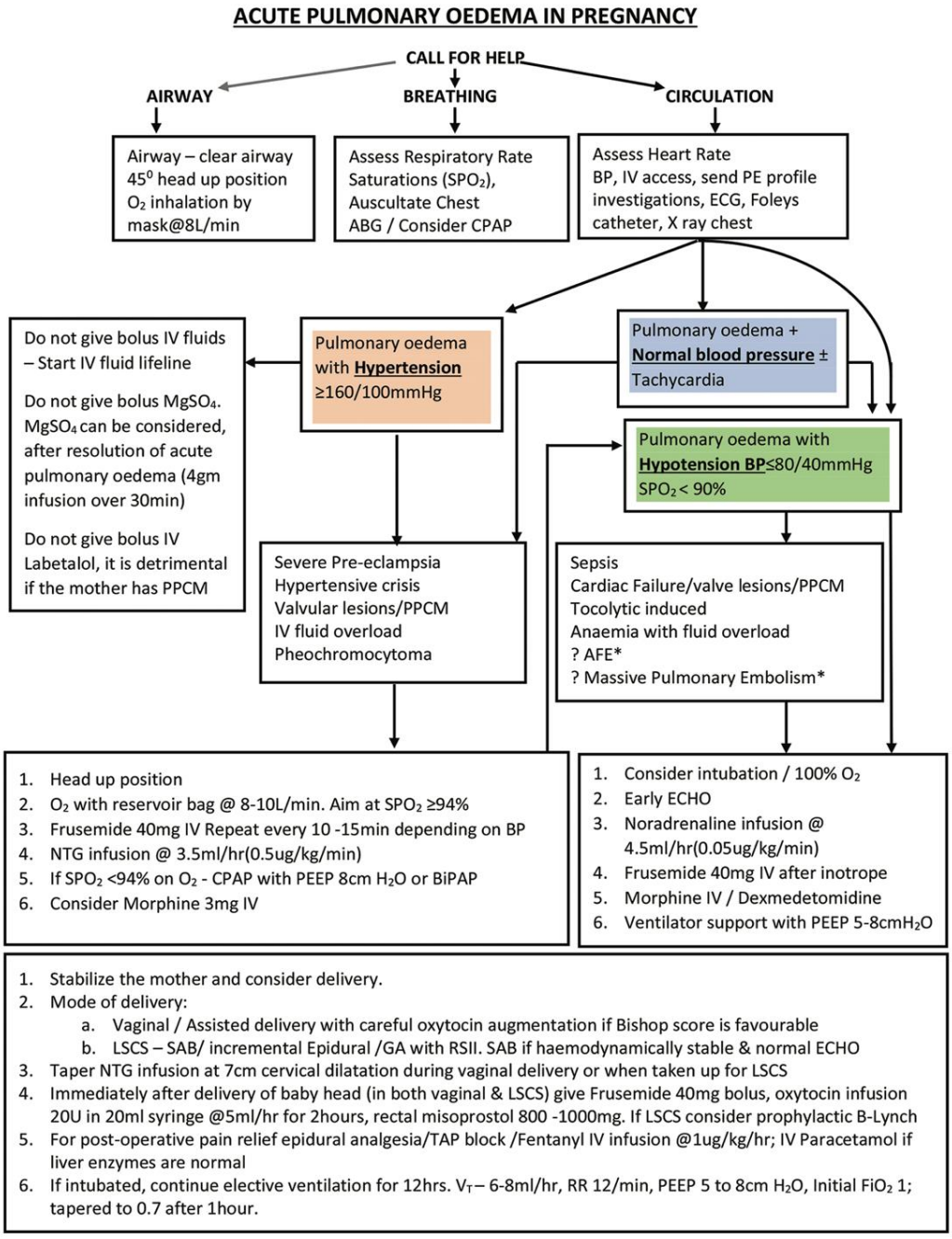

Figure 3. Management Pathway of Acute Pulmonary Oedema in Pregnancy (10)

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Preeclampsia is a frequent cause for obstetric patients to be admitted to the intensive care unit (ICU), and ALO can pose a life-threatening risk for those with preeclampsia (11,12) In our case, a 30-year-old woman was diagnosed with G7P1A5 gravida 29–30 weeks with severe preeclampsia, acute respiratory distress syndrome (ARDS) due to ALO. According to the American College of Obstetricians and Gynecologists (ACOG), patients suffering from severe preeclampsia should terminate the pregnancy, particularly if the pregnancy has reached 34 weeks or if the mother's condition has been stabilized (13). Terminating the pregnancy was our principal treatment. Since the mother's condition was unstable, the termination was postponed and efforts were made to stabilize the mother.

The aim of treating pulmonary oedema during pregnancy is to reduce preload and afterload on the left ventricle, reduce and prevent myocardial ischemia, maintain adequate ventilation and oxygenation, and protect against the risk of infection. The ABCDE principle remains important in treatment algorithms. Airway management should be carried out considering the high risk of heart attack in patients. Non-invasive ventilation should be performed before tracheal intubation to increase inspiratory volume, allow fluid movement from the alveoli to the lungs, reduce the respiratory effort to prevent fatigue and reduce the risk of tracheal intubation. Non-invasive ventilation also helps prevent complications of tracheal intubation during pregnancy, especially in pregnant women with preeclampsia such as intracerebral bleeding (14,15). ALO requires prompt oxygenation, ventilation, and circulation control. The patient's hemodynamic status at presentation (hypertension, normal blood pressure, or hypotension) determined etiological reasons and treatment (3,13–15)

Ventilatory and non-ventilatory methods have been utilized to treat pregnancy-related acute respiratory distress syndrome. There are different ways to ventilate, such as lung-protective mechanical ventilation, oxygenation, sufficient PEEP, prone ventilation, extracorporeal membrane oxygenation, airway pressure release ventilation, and recruitment maneuvers. Non-ventilatory strategies include fluid restriction, neuromuscular inhibition, corticosteroids, and inhaled prostacyclin/nitric oxide. Meanwhile, the strategy that offers the potential to decrease mortality in ARDS is the use of lung-protective mechanical ventilation (14)

The patient received oxygen with an NRM of 15 lpm before intubation. Nevertheless, the patient's saturation failed to improve, leading to respiratory acidosis, necessitating intubation. Fluid treatment was also administered. Monitoring is conducted to prevent the occurrence of excessive fluid, which could exacerbate the patient's disease. Within 8 hours, we promptly reached our intended therapeutic goals. These goals including keeping tidal volume to 6 to 8 mL/kg (ideal body weight). Hold PaCO2 below 60 mm Hg if at all feasible. Trim plateau pressures to between 30 and 35 cmH2O. Maintain PaO2 ≥ 55 mm Hg and SpO2 ≥ 88% as long as electronic FHR tracing is reliable. In individuals with a non-reassuring fetal state, a greater PaO2 may be required. Provide sufficient PEEP and titrate according to the requirement for oxygen.

The initial PaO2 in our patient was 70 mmHg, PCO2 was 109.7 mmHg, and oxygen saturation was 63% with NRM at 15 liters per minute. During the subsequent examination, the PaO2 level increased to 147mmHg, PCO2 decreased to 39.2mmHg, and oxygen saturation reached 98% AC PC Pi 19 RR 16 PEEP 8 FiO2 60%.

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We used propofol as sedatives, fentanyl, and rocuronium. Aside from that, furosemide is prescribed as a venodilator and diuretic. Propofol is widely used as a general anesthetic in pregnant women for both obstetric and non-obstetric procedures. It has not been linked to major fetal abnormalities in doses that are considered safe by doctors. Propofol was classified as FDA Pregnancy Category B. Propofol was found to lower the production of PGE2, COX2, interleukins, and tumor necrosis factor. These chemicals are normally made by amniotic epithelial cells that come from the inside of the placenta. This has a protective effect against starting labor too early (16). Multiple studies have found that low doses (2 mg/kg) of propofol result in equivalent Apgar ratings as well as neurological and adaptive capacity scores (17). In our case, we only administer less than 2 mg/kg propofol to the patient, which is a modest dose. There is no evidence of propofol's teratogenicity in animals or humans; nonetheless, there are concerns regarding neonatal depression when it is administered near to birth, particularly at high dosages (>9 mg/kg) (16,17)

Rocuronium was designated as FDA Pregnancy Category B, and it is not known to cause skeletal muscular weakness or paralysis in the neonate. When delivered in clinically meaningful doses, the water-soluble and positively charged highly ionized molecules of both depolarizing and nondepolarizing neuromuscular blocking medicines efficiently impede transfer across the placental barrier (18).

Opioids were classified as FDA Pregnancy Category C drugs, except for oxycodone which was categorized as Category B (16)A study on Intravenous patient-controlled analgesia comparing remifentanil with fentanyl revealed that remifentanil is more frequently related to temporary maternal oxygen desaturation, while fentanyl is linked to a greater requirement for neonatal resuscitation (16,19). While, fentanyl can easily pass through the placenta, more research is needed to determine its potential to predispose a fetus to opioid dependency in the womb (19). In our case, the top priority is to save the mother, hence the use of fentanyl is prioritized.

A comprehensive assessment is there after conducted on the patient. The echocardiography results indicated satisfactory left ventricular systolic function, with an ejection fraction (EF) of 49%. As per the guidelines of the European Society of Cardiology (ESC), it is recommended that all patients in ALO undergo evaluation using echocardiography. This test should include finding the left ventricular ejection fraction (LVEF), looking for segmental kinetic abnormalities (like those caused by ischemic factors), analyzing the right ventricular (VD) function, which includes figuring out the pulmonary artery pressure, checking the diastolic function of the left ventricle, and looking for signs of possible valvular disease. Echocardiography plays a crucial part in patient management since it immediately influences the decisions made regarding patient care. Furthermore, echocardiography serves as a valuable technique for determining the cause of sudden pulmonary edema, as well as evaluating any associated complications and predicting the outcome (20)

Once the patient's condition stabilized, 12 hours after being in a stable state, termination of pregnancy was performed on the patient under general anesthesia. The baby was born with an APGAR SCORE of 4/6 with a birth weight of 1100 grams. Postoperatively the patient was sedated in the ICU with ETT retention.

The patient was subsequently hospitalized for 2 days in the Intensive Care Unit (ICU) and showed improvement.

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According to the Protocol-based Management of Acute Pulmonary Edema in Pregnancy, if the patient was already intubated before the termination, it is recommended to continue elective breathing for 12 hours. The tidal volume is set at 6-8 mL per hour, the respiratory rate is 12 bpm, PEEP 5 to 8 cm H2O, Initial FiO2 1; tapered to 0.7 after 1 hour.[14] The following day, the patient's condition had improved and stabilized, and weaning procedures were carried out. We conducted extubation 20 hours after the surgery. After 24 hours of extubation, we transferred the patient to a standard hospital ward.

CONCLUSION

Due to physiological changes and fluid overload, pregnancy-related pulmonary edema is challenging. First, stabilize the mother and consider the fetus. This case's therapy centered on lowering left ventricle preload and afterload, preserving ventilation and oxygenation, and preventing infection. Treatment plans were based on the ABCDE idea, which stressed controlling the airway and non-invasive breathing to avoid problems with tracheal intubation, especially in women who are preeclamptic. Lung-protective mechanical ventilation, oxygenation, and fluid restriction were used. Echocardiography was essential for heart function evaluation and patient management. Due to their pregnancy safety, propofol, fentanyl, and rocuronium were provided cautiously. It was crucial to monitor maternal and fetal parameters throughout the process. According to guidelines, severe preeclampsia should be terminated after 34 weeks or when the woman stabilizes. Following surgery, the patient was treated in the ICU according to the pregnant ALO protocol. This example shows the need for multidisciplinary collaboration, evidence-based standards, and tailored patient care in handling difficult obstetric crises like ALO in preeclampsia patients.

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

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Authors' Contributions

All authors have contributed to all processes in this research.

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Literature Review

THE DIFFERENTIATING OF SEPSIS-ASSOCIATED AND SEPSIS-INDUCED ACUTE KIDNEY INJURY IN INTENSIVE CARE UNIT PATIENTS

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a severe and common complication in Intensive Care Unit (ICU) patients, commonly resulting from sepsis. It is associated with elevated mortality, chronic renal failure, and other long-term consequences. Sepsis-associated AKI (SA-AKI) and Sepsis-induced AKI (SI-AKI), a specific sub-phenotype, differ in their underlying pathophysiology. **Objective:** To examine the distinctions between SA-AKI and SI-AKI, focusing on their pathophysiology, biomarkers for detection, and associated prognoses in critically ill patients. This literature review examines the findings of randomized control trials (RCTs) or meta-analysis studies that learn about biochemical mediators and biomarkers for SA-AKI and SI-AKI, including NGAL, Kim-1, and others, as well as the prognostic impact of these conditions. The literature was gathered from Google Scholar and PubMed using the keywords Sepsis-Associated Acute Kidney Injury, Sepsis-Induced Acute Kidney Injury, Intensive Care Unit, and Sepsis and published within the last ten years (2018–2023). Articles unavailable in the full text were excluded. **Review:** SA-AKI and SI-AKI are distinct entities within the broader spectrum of sepsis and AKI. SI-AKI involves sepsis-induced direct kidney damage, which differentiates it from other forms of SA-AKI. Various biomarkers such as NGAL, Kim-1, and others are crucial for early detection and differentiation between these conditions. Patients with SA-AKI and SI-AKI usually have a bad outlook. They are more likely to die, be disabled for a long time, and need longer stays in the ICU and hospital than patients with sepsis or AKI alone. Figuring out the underlying pathophysiology and using the right biomarkers can help with early diagnosis and could lead to better outcomes for patients through targeted therapies. **Summary:** SA-AKI and SI-AKI represent critical complications in ICU patients with sepsis, leading to high mortality and long-term adverse outcomes. Differentiating between these conditions using biomarkers is essential for early detection and management. These patients have a worse prognosis than those with sepsis or AKI alone. This shows how important it is to keep researching and finding better ways to treat these serious complications in critically ill patients.

Keywords: Acute Kidney Injury; Intensive Therapy; SA-AKI; SI-AKI; Sepsis

ABSTRAK

Pendahuluan: Cedera Ginjal Akut (Acute Kidney Injury/AKI) adalah komplikasi yang umum dan parah pada pasien ICU, yang sering kali disebabkan oleh sepsis. Hal ini dikaitkan dengan angka kematian yang tinggi, gagal ginjal kronis, dan konsekuensi jangka panjang lainnya. AKI terkait sepsis (SA-AKI) dan AKI yang diinduksi sepsis (SI-AKI), sebuah subfenotipe spesifik, berbeda dalam patofisiologi yang mendasarinya. **Tujuan:** Untuk membedakan antara SA-AKI dan SI-AKI, dengan fokus pada patofisiologi, biomarker untuk deteksi, dan prognosis terkait pada pasien yang sakit kritis. Tinjauan pustaka ini merupakan tinjauan naratif yang mengkaji hasil uji coba terkontrol acak (RCT) atau studi metaanalisis yang mempelajari mediator biokimia dan biomarker untuk SA-AKI dan SI-AKI, termasuk NGAL, Kim-1, dan lainnya, serta dampak prognostik dari kondisi ini. Literatur dikumpulkan melalui Google Scholar dan PubMed dengan menggunakan kata kunci Sepsis-Associated Acute Kidney Injury, Sepsis-Induced Acute Kidney Injury, Intensive Care Unit, dan Sepsis dan diterbitkan dalam sepuluh tahun terakhir (2018–2023). Peneliti mengecualikan artikel yang tidak tersedia secara lengkap. **Review:** SA-AKI dan SI-AKI adalah entitas yang berbeda dalam spektrum sepsis dan AKI yang lebih luas. SI-AKI melibatkan kerusakan ginjal langsung yang diinduksi sepsis, yang membedakannya dengan bentuk SA-AKI lainnya. Berbagai biomarker seperti NGAL, Kim-1, dan lainnya sangat penting untuk deteksi dini dan diferensiasi antara kondisi-kondisi ini. Prognosis pasien dengan SA-AKI dan SI-AKI umumnya buruk, dengan kemungkinan kematian

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yang lebih tinggi, kecacatan jangka panjang, dan rawat inap di ICU dan rumah sakit yang lebih lama dibandingkan dengan pasien dengan sepsis atau AKI saja. Memahami patofisiologi yang mendasari dan menggunakan biomarker yang tepat dapat membantu diagnosis dini dan berpotensi meningkatkan hasil akhir pasien melalui terapi yang ditargetkan. **Rangkuman:** SA-AKI dan SI-AKI merupakan komplikasi kritis pada pasien ICU dengan sepsis, yang mengarah pada kematian yang tinggi dan hasil jangka panjang yang merugikan. Membedakan antara kondisi ini dengan menggunakan biomarker sangat penting untuk deteksi dini dan manajemen. Prognosis untuk pasien-pasien ini lebih buruk dibandingkan dengan pasien dengan sepsis atau AKI saja, menggarisbawahi perlunya penelitian lanjutan dan strategi terapi yang lebih baik untuk mengurangi komplikasi parah pada pasien yang sakit kritis.

Kata kunci: Cedera Ginjal Akut; Terapi Intensif; SA-AKI; SI-AKI; Sepsis

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INTRODUCTION

Over half of the patients in intensive care units (ICUs) around the world experience Acute Kidney Injury (AKI), with sepsis being the most common underlying cause. Epidemiological studies indicate that AKI is associated not only with acute severe effects but also with significant long-term consequences. Although patients may recover from AKI, they remain at risk of developing recurrent kidney injuries (1,2).

Sepsis-associated AKI can manifest in a variety of phenotypes and prognoses (3). Patients with AKI and those meeting the consensus criteria for sepsis are considered to have Sepsis-Associated Acute Kidney Injury (SA-AKI). Meanwhile, Sepsis-Induced Acute Kidney Injury (SI-AKI) can be seen as a sub-phenotype of SA-AKI, where mechanisms induced by sepsis produce direct kidney damage (1). The prognosis for SA-AKI and SI-AKI events is worse compared to sepsis and AKI separately (4). There are still a lot of questions that need to be answered about definitions, epidemiology, pathophysiology, how to diagnose, how to treat, and how extracorporeal and new therapies affect patients (5).

SA-AKI is defined as AKI occurring within seven days of a sepsis diagnosis. It is further categorized into early SA-AKI, which develops within 48 hours of sepsis diagnosis, and late SA-AKI, which arises between 48 hours and seven days. The proposed seven-day window is based on the observation that AKI typically develops within a few days following the onset of sepsis. Beyond this period, AKI is generally considered less likely to be directly related to the initial sepsis event. The difference between early and late SA-AKI is important because late-stage AKI progression has worse clinical outcomes and a higher death rate than early-stage AKI. Phenotyping for focused assessment and management can be improved by distinguishing between the early and late phases of SA-AKI. Untreated or early sepsis patients are at a higher risk of experiencing SI-AKI, whereas those who get sepsis-related treatments are more prone to developing SA-AKI. Additional variables may also contribute to the development of AKI (1).

REVIEW

Pathogenesis

Sepsis is marked by an overproduction of many pro-inflammatory cytokines and is linked to malfunction in multiple organs. SI-AKI is distinguished by a fast rapid loss of kidney function, as indicated by elevated creatinine and Blood Urea Nitrogen (BUN) levels, as well as reduced Glomerular Filtration Rate (GFR) and urine production. Multiple factors can

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contribute to SI-AKI, such as systemic inflammation and immune system dysregulation, hemodynamic change, activation of the complement system, dysregulation of the renin-angiotensin-aldosterone system (RAAS), dysfunction of mitochondria, metabolic reprogramming, and dysfunction of the microcirculatory system. Various factors can indirectly contribute to SA-AKI, such as nephrotoxic drugs, hyperchloremia, and abdominal compartment syndrome (1,6).

Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) are released following the invasion of a pathogen. These patterns attach to groups of receptors known as pattern recognition receptors, with one example being Toll-Like Receptors (TLRs).

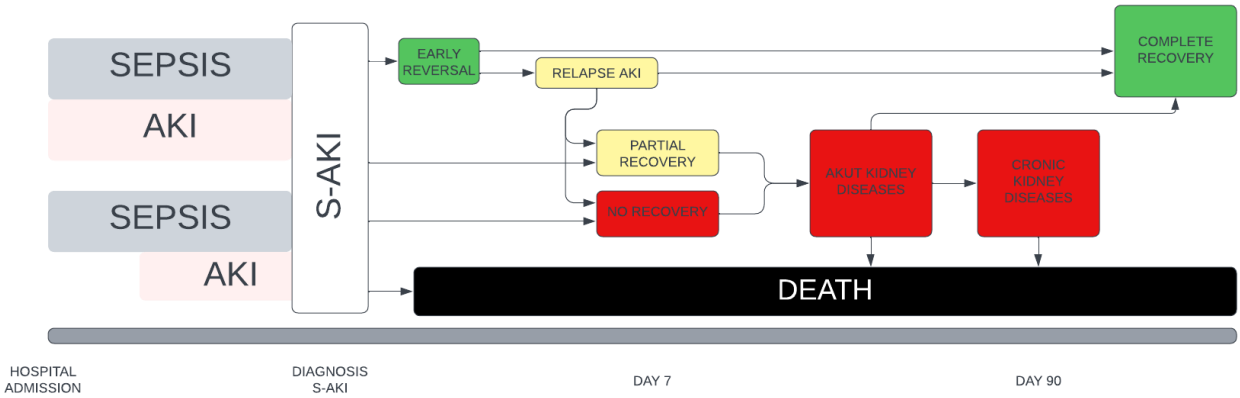

Figure 1. The Clinical Progression and Outcome of Sepsis-Associated Acute Kidney Injury (SA-AKI) (The exact timing of renal injury onset in sepsis is unclear. Patients who come with sepsis probably have AKI, and conversely, patients who come with AKI also definitely have sepsis. AKI may coexist with sepsis at the time of hospital admission; (a) or develop during treatment; (b). S-AKI may improve early in the first week after diagnosis and is linked to a favorable prognosis. AKI can develop within the first 7 days, leading to permanent damage and progressing to SA-AKI. During this period, patients may achieve full or partial recovery, but some may suffer ongoing injury without improvement. In the long term, this lack of recovery can lead to chronic kidney disease (CKD))

Toll-like receptors (TLRs) are present on the plasma membrane of immune cells, endothelial cells, and tubular epithelial cells (TEC). The binding process results in the overproduction of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-18, TNF-α, chemokines, and Reactive Oxygen Species (ROS), while also activating the complement system. Uncontrolled immune response and extensive inflammation play a crucial role in the development of septic AKI (6,7).

The Renal Blood Flow (RBF) is the sum of cardiac output and the effective circulatory volume. During the onset of sepsis, there is an initial rise in cardiac output, followed by a progressive decline as a result of septic damage. Multiple studies have discovered that RBF remains stable or may even be elevated during the early stages of septic AKI (8). These findings suggest that renal hypoperfusion is not necessary for septic AKI to occur. Vasodilation is caused by endothelial dysfunction in the

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kidney blood vessels and the release of vasoactive substances like nitric oxide (6,8–10). Multiple studies have shown that sepsis can present with microcirculatory changes even without macrocirculatory alterations (11). These findings suggest that changes in microvascular hemodynamics may contribute to the development of SI-AKI.

The renal blood vessels consist of renal arteries, glomerular microvasculature, and peritubular capillaries. Endothelial cells primarily regulate the homeostasis of RBF and microvascular permeability. Alterations in the interaction among endothelial cells result in heightened capillary permeability and leukocyte secretion. Prior research has shown that endothelial nitric oxide synthase (eNOS) levels drop in a septic model induced by Cecal Ligation and Puncture (CLP), and this enzyme plays a crucial role in vasodilation (12).

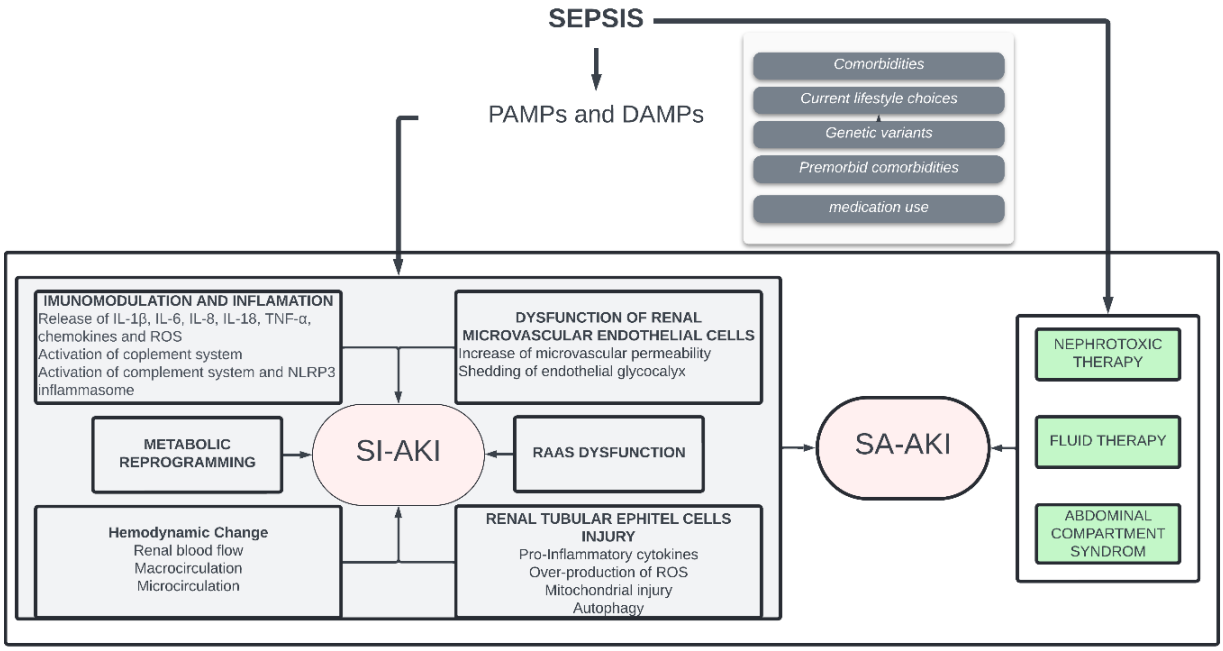

Figure 2. Pathogenesis of Sepsis AKI

(The release of PAMPs, like lipopolysaccharides, and DAMPs from damaged cells and tissues can trigger the activation of a dysfunctional immune response, which is characteristic of sepsis. The underlying susceptibility to tissue and organ damage varies among individuals, influenced by non-modifiable factors such as comorbidities, lifestyle choices (e.g., smoking), genetic variations (e.g., single nucleotide polymorphisms), pre-existing health conditions, and medication use (e.g., renin-angiotensin-aldosterone system inhibitors for blood pressure control). Additionally, modifiable factors, such as the use of vasopressors, mechanical ventilation, or the presence of bacteremia, also play a role. 1) imbalanced immune response and widespread inflammation, including the release of pro-inflammatory cytokines; 2) hemodynamic alterations, including changes in renal blood flow, macrocirculation, and microcirculation; 3) dysfunction of renal microvascular endothelial cells; 4) Renal tubular epithelial cell damage mediated by the TLRs/NF-κB signaling pathway and a decline in autophagy during the later stages of sepsis; 5) RAAS dysfunction and 6) metabolic reprogramming play a role in the occurrence of SI-AKI. Other sepsis-related factors indirectly contribute to AKI. These include the use of nephrotoxic therapies, fluid therapy, and abdominal compartment syndrome)

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Endothelial glycocalyx shedding was observed in all sepsis patients, along with a rise in soluble glycocalyx components in the plasma. The damage to the endothelium and the loss of the glycocalyx cause leukocyte leakage and platelet aggregation, leading to a decrease in blood flow velocity. This can result in the development of microthrombi and subsequent blockage of capillaries (7). Therefore, renal blood vessel endothelial cells are major contributors to SI-AKI development.

Acute TEC injury frequently happens in cases of SI-AKI. TLRs, specifically TLR2 and TLR4, are present in TECs. The apical membrane of TECs contains TLRs that recognize PAMPs and DAMPs. When these molecules bind to the TLRs, it triggers the activation of Nuclear Factor kappa B (NF-κB). This activation leads to the release of an excessive amount of pro-inflammatory cytokines, the generation of ROS, and harm to the mitochondria. Autophagy in proximal tubules was found to be temporarily enhanced largely 3 hours after CLP, as evidenced by the utilization of angiotensin-converting enzyme, a marker specific to proximal tubules. Nevertheless, autophagy was observed to decline between 9 and 18 hours, coinciding with the occurrence of kidney damage both in terms of pathology and function (6,9). Decreased autophagy in the late phases of sepsis may potentially contribute to proximal TEC dysfunction, according to these results.

Early Detection and Diagnosis

The diagnosis of AKI according to KDIGO has certain limitations due to a lack of consensus on determining a baseline blood creatinine level (13,14). Delayed alterations in serum creatinine levels are frequently observed, particularly in cases of sepsis. When there is damage to the kidney parenchyma, it can impact up to 50% of the kidneys without causing a rise in creatinine levels (15,16). Presently, numerous research document early diagnostic indicators for AKI. Distinct biomarkers have unequivocally demonstrated their ability to signal different damage pathways. Integrating injury/stress markers with functional assessments provides a more comprehensive and extensive quantity of information compared to utilizing them individually (7,17). The process cohort study found that the occurrence of positive-biomarker AKI was associated with a worse 30-day survival rate compared to negative-biomarker AKI (18). Table 1 and Table 2 show biomarkers for detecting SA-AKI based on ADQI 28.3.

Table 1. Renal Injury Mechanisms and Biomarkers (8,19)

Mechanism	Biomarkers
Ischemia	NGAL, Kim-1, MCP-1, and cry61
Hypoxia	L-FABP
Cell-cycle arrest	TIMP-2, IGFBP 7

Table 2. Location of Kidney Injury and Biomarkers (8,19)

Location	Biomarkers
Glomerulus	Urin: β2-microglobulin, Albumin, TP (total protein), and α1-microglobulin Blood: creatinine, NGAL, and cystatin C
Proximal tubule	Kim-1, L-FABP, NET-3, NAG, netrin-1, IL-18, HGF, IGFBP 7, and TIMP-2
Distal tubule	NGAL, GST-α/π, cystatin C, Cyr61, and NET-3
Choledochal duct	Calbindin D28

Recent Advances in Biomarkers as Predictors for SI-AKI

The details on the recent advancements in biomarkers used as predictors for SI-AKI are provided in Table 3. By using these biomarkers in a clinical setting, early damage to the parenchymal structure of the kidney can be

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found, without having to wait for signs of renal failure to show up (9,20).

Therapeutic Approaches to S-AKI

The basic principle for treating sepsis patients is typically prompt administration of the right medicines along with source control. Plasma perfusion, renal replacement therapy (RRT) with or without hemoperfusion, nutritional support with protein and calorie supplements, managing fluid balance, keeping acid-base and electrolyte balance, and making sure hemodynamic stability are the main treatments used currently. Carefully used nephrotoxic drugs such as aminoglycosides, amphotericin B, and vancomycin especially when combined with piperacillin-tazobactam can prevent kidney damage (6,7,13,17). The initial therapeutic goals include maintaining a central venous pressure of 8–12 mmHg, a mean arterial pressure (MAP) of 65 mmHg, a urine output of 0.5 ml/kg/hour, and a central venous oxygen saturation of 70% (13,21–23).

Antibiotic Therapy

Within an hour after the diagnosis of sepsis, broad-spectrum antibiotics should be given (6,10,24). In the meantime, the septic source needs to be located to administer the proper antibiotic therapy. Certain medications, including aminoglycosides, amphotericin B, and vancomycin, have nephrotoxic effects and should be used with caution. Early AKI development is linked to delayed antibiotic therapy (6).

Fluid Resuscitation

Patients with sepsis or septic shock should begin resuscitation and treatment immediately to prevent damage to the macro and microcirculation, according to the Surviving Sepsis Campaign (SSC) 2021. Within the first three hours after resuscitation, it is suggested to administer crystalloid fluid intravenously at a rate of 30 mL/kg as the initial option. Monitoring is needed to avoid fluid excess during resuscitation (25,26). Isotonic crystalloid fluid is recommended for people who are susceptible to AKI. This is still up for dispute, though. Excessive doses of 0.9% saline have been linked to pro-inflammatory cytokine release, renal vasoconstriction, hyperchloremic metabolic acidosis, and disturbance of natural coagulation pathways (27). This can lead to AKI in patients and worsen the patient's condition (15,27–29). At the same time, the use of hydroxyethyl starch (HES) and gelatin solutions raises the risk of AKI and mortality (7).

Vasoactive Agents

Vasopressors should be started when fluid resuscitation is not sufficient (30). The SSC 2021 recommends norepinephrine as the first-line vasopressor for septic shock (25). Vasopressin and Septic Shock Trial (VASST) showed similar results and no more harmful effects in any of the patients who were tested with norepinephrine or vasopressin. Vasopressin and Septic Shock Trial (VASST) revealed comparable results and no increased adverse effects in any of the patients under investigation using norepinephrine or vasopressin. Additionally, vasopressin has fewer adverse effects on the kidneys than dopamine (1,30–32). The administration of vasopressors, such as terlipressin or vasopressin, appears to increase urine production and creatinine clearance similarly. Less is known, though, about the impact of raising MAP to values over 60–65 mmHg. Urine output was found to be enhanced by raising MAP from 65 to 75 mmHg in certain studies, however, raising MAP to values above 85 mmHg did not yield any further advantages. Several other studies were unable to

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demonstrate the advantages of raising RPP to values above 65 mmHg (11,33,34).

Renal Replacement Therapy (RRT)

Renal Replacement Therapy (RRT) has been used for the management of AKI, and numerous research findings indicate that RRT might be advantageous for some patient populations (35). However, recent research reports that RRT provides limited effects on AKI patient recovery (36). Eighty patients in a French multicenter trial with an initial blood creatinine level of 188 µmol/L were given conservative care or hemofiltration for 96 hours (25 mL/kg/hour) within 24 hours of organ failure owing to sepsis. Early initiation, occasionally in the absence of SA-AKI, had unfavorable effects, such as increasing organ failure. Following this, 620 patients were randomly assigned. Three hundred and eleven patients in the early strategy group and thirty-eight patients in the delayed strategy group died on day sixty. However, Kaplan-Meier estimates of mortality did not show a significant difference between the two groups. In the delayed strategy group, kidney replacement therapy was not administered to 151 patients or 49% of the total. Compared to the delayed strategy group, the early strategy group experienced higher rates of catheter-related bloodstream infections (10% vs. 5%). In the delayed strategy group, diuresis a sign of better kidney function occurred earlier (6,37).

There is controversy regarding when to initiate RRT (35,36,38–42). According to the KDIGO criteria, early initiation of RRT is recommended for stage 3 AKI or if any of the following criteria that shown in table 3 (13,38,39). However, recent studies state that early dialysis initiation based solely on the AKI stage has not proven beneficial in reducing mortality (38). The recommended RRT dose is 20-25 ml/kg/hour (21).

Table 3. Recent Biomarkers Used as Predictors for SI-AKI

Biomarkers	Description
sTREM-1	sTREM-1 refers to the dissolved form of the triggering receptor expressed on myeloid cells 1, which is specifically monocytes and neutrophils. TREM-1 is a receptor belonging to the immunoglobulin superfamily that is involved in infl the occurrence of AKI, the presence of sTREM-1 can be identified in the urine of the patient. However, it is impor sTREM-1 in the urine is not correlated to its concentration in the serum (9,20).
NGAL	Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein that belongs to the lipid-binding protein superfamily. It is found on the surface of neutrophils. NGAL expression in the kidney is tightly controlled within 3 hours of an ischemic injury. Between 24 and 48 hours after the injury, the level of NGAL mRNA expression peaks, rising by over 1000 times (9,20).
Cell-Cycle Arrest Protein	Tissue inhibitor metalloproteinase-2 (TIMP-2) is a 21-kDa protein that is non-glycosylated. It is composed of 194 amino acid residues and has a role in controlling cell proliferation and programmed cell death. Urinary insulin-like growth factor-binding protein 7 (IGFBP7) is a 29-kilodalton glycoprotein that belongs to the IGFBP superfamily. AKI patients have higher levels of TIMP-2 and IGFBP7 in kidney tubular cells. This stops the G1 cell cycle by turning on p27KIP1 and p21. Testing the levels of TIMP-2 or IGFBP7 in urine can predict the onset of acute kidney injury (AKI) at an early stage (9,20).
KIM-1	Kidney Injury Molecule-1 is a type 1 transmembrane glycoprotein. In ischemia and nephrotoxic AKI, KIM-1 expression is controlled in the kidney's proximal tubular cells. Using immunological techniques, the extracellular portion of KIM-1 may be isolated from proximal tubular cells and identified. Urinary KIM-1 has a sensitivity of 74.0% and specificity of 86.0% for AKI prediction (9,20).
Netrin-1	Netrin-1's original description states that it can affect axonal migration and the development of the central nervous system during neurogenesis processes. Netrin-1 is mostly found in the kidneys, and finding netrin-1 early in the urine has been linked to renal tubule ischemia-reperfusion injury. Urinary netrin-1 increased 2 hours after cardiopulmonary bypass (CPB), peaked at 6 hours, and continued to grow up to 48 hours after CPB, while creatinine increased only after 48 hours. This information was reported in a study on AKI associated with CPB (9,20).

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Emerging Therapeutic Approaches

Studies have demonstrated that implementing early goal-directed therapy can enhance the chances of survival in patients with sepsis. However, death rates for SI-AKI continue to be elevated. Autophagy activation in proximal tubular epithelial cells (TEC) decreases during the later stages of sepsis. Various drugs have been identified as beneficial in treating S-AKI by promoting autophagy. Additionally, several phytochemicals, known for their anti-inflammatory and antioxidant properties, are considered promising complementary treatments for sepsis-induced acute kidney injury (SI-AKI). Various natural plants contain bioactive compounds that have been found to exhibit anti-tumor, anti-infective, anti-inflammatory, immunomodulatory, and neuroprotective properties. Resveratrol, moringa isothiocyanate-1, rhizoma Coptidis extracts, curcumin, zingerone, and glycyrrhizic acid are some of the substances that can lower oxidative stress and stop inflammation. These substances also decrease the production of IL-1β, IL-6, and TNF-α (6). Additionally, angiotensin II, a potent vasoactive agent, may be beneficial for SA-AKI patients (41).

Angiotensin II

Angiotensin II induces a substantial elevation in MAP within the initial three hours. In the angiotensin II group, 69.9% of patients experienced an increase in MAP, while only 23.4% of patients in the placebo group showed an increase. There was no discernible disparity in the rates of mortality that occurred while patients were still in the hospital. A study of a small group of patients who received RRT showed that those who were given angiotensin II needed less RRT and had a higher chance of living until day 28. If these findings are confirmed in a broader group of individuals, angiotensin II could potentially serve as a novel therapy for SA-AKI (17).

Alkaline phosphatase

Alkaline phosphatase is a naturally occurring enzyme in the body that detoxifies by removing phosphate groups from various molecules (43). Giving systemic alkaline phosphatase has been shown to protect against SA-AKI in both preclinical and small clinical studies (44,45). Administering alkaline phosphatase intravenously enhances the natural process of clearing creatinine from the body and is linked to reduced levels of kidney tubular damage markers. Importantly, this treatment does not lead to a decrease in the need for RRT (46). A 2020 meta-analysis found that alkaline phosphatase shows a relatively slow protective effect by increasing Endogenous Creatinine Clearance (ECC) on days 7, 14, and 28. ECC improved when patients were given 0.212 mg/kg alkaline phosphatase. Mortality was higher at days 28 and 90 in patients who were administered 1.6 mg/kg of alkaline phosphatase (47). Further research is needed on the positive effects of using alkaline phosphatase in SA-AKI patients.

Thiamine

Thiamine (B1 vitamin) levels can be reduced by increased metabolic demand, parenteral or enteral feeding, diuretics, as well as hemodialysis and hemofiltration. About 20 – 70% of patients with septic shock had thiamine deficiency (48). A possible cause of kidney injury in sepsis could be mitochondrial dysfunction, which refers to the inability of cells to effectively extract and utilize oxygen for aerobic metabolism, even when there is sufficient oxygen supply. In the absence of thiamine, pyruvate is unable to participate in the Krebs cycle, resulting in the conversion of pyruvate into lactate instead of acetyl-

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coenzyme A. Consequently, a lack of thiamine causes a change in the body's metabolic process towards the anaerobic pathway, leading to elevated levels of lactate in the blood, cell death, organ damage (including renal failure), and the possibility of death (48–51). A secondary analysis was done on a randomized controlled trial (RCT) with 70 people who had septic shock. These people were randomly assigned to receive either 200 mg of thiamine through an IV twice a day for 7 days or a placebo. The analysis revealed that the patients who got thiamine had lower levels of serum creatinine and a decreased likelihood of developing RRT (52). Another study stated that thiamine did not show a benefit in-hospital mortality. However, this drug may be considered for use in patients with kidney dysfunction (48). It is not possible to draw definitive conclusions, highlighting the need for further research, particularly in patients with thiamine deficiency (43).

SUMMARY

Acute Kidney Injury (AKI) is prevalent among ICU patients, with sepsis being a common cause. Sepsis-associated AKI (SA-AKI) and its subset, Sepsis-Induced AKI (SI-AKI), pose significant challenges, carrying worse prognoses than sepsis or AKI alone. The differentiation between early (within 48 hours) and late (48 hours to 7 days) SA-AKI is crucial for understanding outcomes, as later stages are linked to higher mortality. SI-AKI happens when systemic inflammation, immune system dysregulation, microvascular dysfunction, and injury to renal tubular epithelial cells (TEC) all work together in a complicated way. Pro-inflammatory cytokines and Reactive Oxygen Species (ROS) play significant roles. Kidney damage is caused by things like endothelial dysfunction and changes in the microcirculation. These changes affect both the large and small blood vessels in the kidneys. Pathogen recognition receptors, such as Toll-Like Receptors (TLRs), have a direct effect on TECs. This causes the NF-κB pathway to be activated and autophagy to slow down, which makes kidney damage worse. Traditional diagnostic criteria for AKI, such as serum creatinine, have limitations, especially in sepsis. Emerging biomarkers (e.g., NGAL, KIM-1, TIMP-2/IGFBP7) offer earlier detection and better prognostic insights. The combination of injury markers with functional assessments provides a more comprehensive understanding of AKI severity. Prompt administration of broad-spectrum antibiotics is crucial within an hour of sepsis diagnosis. Crystalloid fluids are recommended, with careful monitoring to avoid fluid overload. Hyperchloremic fluids like saline are linked to adverse outcomes, while hydroxyethyl starch (HES) and gelatin are associated with increased AKI risk. Norepinephrine is the first-line vasopressor, with vasopressin as an adjunct. Raising the MAP to 65–75 mmHg can improve outcomes, but higher pressures may not offer additional benefits. While RRT is standard in managing AKI, the timing of initiation remains controversial. Early initiation does not consistently reduce mortality, and delayed strategies may prevent unnecessary RRT. Research into therapies like autophagy activation, phytochemicals, angiotensin II, and alkaline phosphatase is ongoing. These approaches show promise in reducing inflammation, oxidative stress, and kidney damage, offering potential new treatments for SA-AKI. However, further validation in larger clinical trials is necessary.

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Conflict of Interest

The authors affirm that there are no conflicts of interest pertaining to this study.

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Authors' Contribution

Nusi Andreas Hotabilardus contributed to the conceptualization, data collection, data analysis, and interpretation, as well as manuscript preparation; **Novita Anggraeni** was responsible for supervision, critical review, and final approval of the manuscript.

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- Amini S, Najafi MN, Karrari SP, Mashhadi ME, Mirzaei S, Tashnizi MA, et al. Risk factors and outcome of acute kidney injury after isolated cabg surgery: A prospective cohort study. Brazilian J Cardiovasc Surg. 2019; 34(1): 70–5.

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