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Prothrombotic role of antiphospholipid antibodies in a patient with sickle cell disease

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ABSTRACT

Sickle cell disease (SCD) is a common inherited condition in African, Caribbean, and Mediterranean countries. SCD is a hematologic disorder caused by a well-characterized point mutation in the β-globin gene, which produces an abnormal hemoglobin S that results in the sickling of red blood cells in deoxygenated conditions. Patients with SCD display a "hypercoagulation state" leading to an increased risk of severe venous and arterial thrombotic vascular events. Herein we report a case of severe thrombotic complications in a patient with SCD who showed high antiphospholipid antibodies (APA) levels during vascular occlusions.

Keywords: antiphospholipid antibodies; sickle cell disease; hypercoagulation state; thrombotic complications

1. Background

Sickle cell disease (SCD) is characterized by chronic intravascular hemolysis, vascular occlusions, painful and multiple organ damage [1]. It also presents chronic activation of the coagulation system responsible for vaso-occlusive crises and venous thromboembolism (VTE) [2,3]. To date, the frequency of coexisting SCD and APA has not been well evaluated, and most data come from but a few case reports [4,5]. The connection between high APA levels and sickle cell syndrome and its impact on major thrombotic complications of SCD has not been adequately investigated [6]. Interestingly, in our case report, serum APA levels were remarkably high, and we hypothesize that APA may play a prothrombotic role in SCD.

2. Case history

The patient is a 47-year-old Caucasian woman affected by severe SCD, genotype S/S (homozygous sickle cell). Her clinical history was characterized by a mild ischemic stroke episode that occurred at the age of 30 years old, after which she started taking cardioaspirin and was administered monthly transfusion therapy with careful monitoring of HbS. At that time HbS was 45% and Hgb was 7.5 gr/dL, she also performed a transcranial Doppler and cerebral magnetic resonance angiography with evidence of sickle vasculopathy, not moyamoya-like. Given the ferritin levels remained at values of 1500–2000 ng/mL, she underwent iron chelation therapy with deferasirox 20 mg/kg (patient's weight: 80 kg) with satisfactory results.

In October 2019 she suffered a severe stroke and was admitted to the emergency department by her husband, she was found to have altered mental status, right hemiplegia, and aphasia. On triage, the patient had a body temperature of 36.5 °C, blood pressure of 140/80 mmHg, heart rate of 72 beats per minute, respiratory rate of 20 breaths per minute, oxygen saturation of in-room air, and blood sugar of 350 mg/dL. The patient was not articulating or able to communicate history. Physical examination revealed global aphasia, uncooperativeness, left gaze deviation, spastic hypertonus, severe right facial brachial hemiparesis, right hypoesthesia, right spatial inattention, and signs of Babinski on the right. National Institutes of Health Stroke Scale (NIHSS) 19. Initial laboratory investigations revealed severe leukocytosis, normochromic normocytic anemia, elevated reticulocyte count, total bilirubin, lactate dehydrogenase, and a baseline of 42% HbS. An electrocardiogram showed sinus tachycardia. There was no radiographic evidence of acute pulmonary disease on the chest X-ray. A computed tomography (CT) scan without contrast of the head was performed in the emergency department, which did reveal a parenchymal hypodensity area with cortico-subcortical distribution in the left fronto-insular and temporoparietal region with extension to the nuclei of the ipsilateral base; it modestly marked the ipsilateral lateral ventricle.

Therefore, she was admitted to the neurological division unit for a suspected cerebrovascular accident and was given aspirin 125 mg, atorvastatin 80 mg, enoxaparin sodium 6,000 U.I., fondaparinux sodium 2.5 mg/day, mannitol 18% 100 mL × 4/day, and rehydration therapy. The patient was treated with thrombolysis and thrombectomy of the upper and intermediate Sylvian trunk. On day 2, the patient was not alert, oriented, or able to answer questions appropriately. A magnetic resonance imaging (MRI) without contrast of the brain (T2 FLAIR (T2-weighted fluidattenuated inversion recovery)) showed restoration of the flow signal in the context of the left Sylvian axis. A carotid duplex ultrasound revealed less than 50% stenosis of the right internal carotid artery and a normal left internal carotid artery. An echocardiogram showed an ejection fraction of 53% and right ventricular systolic pressure of 88 mmHg, with a negative bubble study and an ischemic pattern of the left ventricular myocardium. The hematology team was consulted on day 3. As the patient was presenting an acute ischemic stroke in the setting of Hb SS disease and hemoglobin on admission was 7.5 g/dL she received 1 unit of packed red blood cells (RBCs). On day 3 the clinical course was complicated by ascending deep vein thrombosis with pulmonary involvement as documented by computed tomography angiography (CTA) in the chest, abdomen, and lower limbs. A thrombophilia screening was performed and an increase in APA values was found with respect to baseline: Lupus anticoagulant (LAC) was detected by Diluted Russell Viper Venom Time (dRVVT); anticardiolipin (aCL) IgG and IgM were respectively 50 GPL/mL by 2.5 GPL/mL and 250 MPL/mL by 15 MPL/mL; IgG and IgM Beta-2-glycoprotein I-1 antibodies (β2GPI-1) were 40 U/mL by 1.5 U/mL and 450 U/mL by 22 U/mL, respectively. In consideration of the new findings, the therapy also included clexane 6000 UI

twice daily (interrupted fondaparinux), methylprednisolone 100 mg twice daily, and gastric protection. On day 4 the patient underwent 4 erythropheresis (ET) procedures using COM.TEC Fresenius cell separator, with Kit PL1. For each procedure performed three days apart from each other, except for the last one performed after a week, about 1200 mL of blood were removed and replaced in two Ets using 3 units, while the other two ETs used 4 units of blood. Fresh leucodepleted blood was used (sampling performed 2/3 days before at most) with HcT 60/62, phenotypically compatible. In each procedure, the exchange was set to arrive at the replacement of the theoretical erythrocyte volume, calculated based on the pre-apheresis hematological values (pre-Hb and pre-HbS).

The procedures were well tolerated, and only minor side effects were noted, specifically episodes of hypocalcemia treated with Ca gluconate. Hemoglobin electrophoresis following exchange transfusions revealed 25.5% HbS with a baseline of 42% HbS on the day of admission. She remained alert and oriented. No neurological deficit was noted. On day 22 she was discharged, went home, and was provided with a follow-up appointment at the clinic. Two months after discharge, the patient arrived at the hematology clinic: neurological symptoms have further improved, deep vein thrombosis is resolving as well as pulmonary embolism, and a repeat blood test revealed stable results, including hemoglobin of 9.6 mg/dL, reticulocyte % of 2.95%, lactate dehydrogenase of 188 U, HbS 25% and APA values returned close to normal range, LAC was absent; aCL IgG and IgM were 28 GPL/mL and 50 MPL/mL, respectively; IgG and IgM β2GPI-1 were 35 U/mL and 25 U/mL, respectively (Figure1).

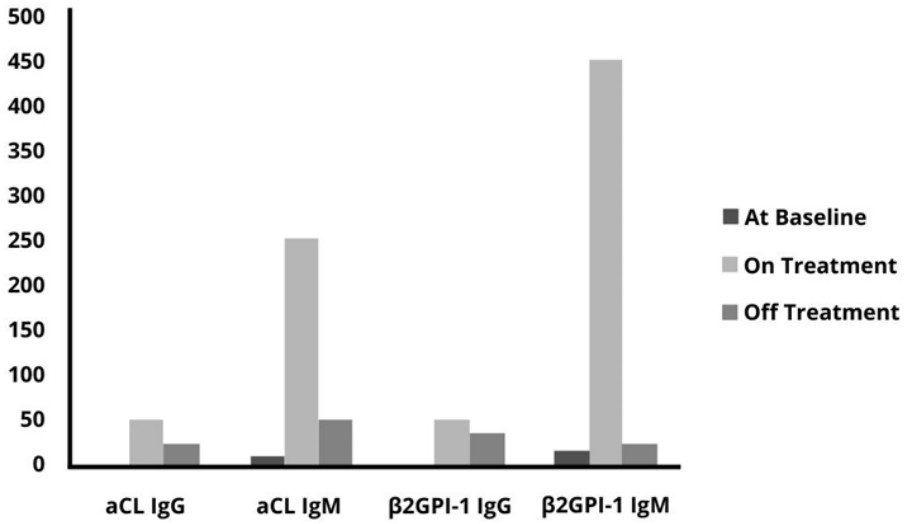

Figure 1. Evolution of changes in anticardiolipin (aCL) IgG and IgM, IgG and IgM Beta 2-glycoprotein I-1 (β2GPI-1) antibodies levels following treatment.

The patient needs neurorehabilitation and continues therapy with cardioaspirin and low molecular weight heparin.

3. Discussion and conclusions

Recent studies strongly suggested that hypercoagulation in SCD is not just a secondary event but contributes directly to the disease pathophysiology [3]. Mechanisms leading to the activation of coagulation are represented by Endothelial and Leukocyte cell Tissue Factor, abnormal activation of thrombin, platelets, and intrinsic coagulation pathway. A few studies have highlighted Circulating Microparticles in SCD patients and these may contribute to thrombin generation by increasing surface phosphatidylserine exposure. Furthermore, anionic phospholipid, including phosphatidylserine, exposure on the surface of erythrocytes occurs during intravascular hemolysis and may induce APA, which supports coagulation activation as a key role in the development of thrombosis in SCD [7].Several studies showed increased levels of APA in SCD patients, especially with homozygous genotype SS [8]. The finding of increased antiphospholipid antibodies in these patients was compatible with the concept that APA formation was associated with structural changes in the red cell membrane that occur in the red cells of patients with sickle cell disease [9].

Merashli et al. systematic review evaluated the relationship between APA and SCD and revealed a statistical link between APA and SCD, but the clinical relevance of APA in SCD remains unclear [10]. Moreover, SCD patients present a defective activation of the alternate complement pathway linked to the consumption of complement factor B which increases the risk of infection and is thought to predispose to autoimmune diseases [11] such as Systemic Lupus Erythematosus SLE and rheumatoid arthritis RA [12,13]. Aygun et al. showed an immune system overstimulation in SCD patients due to multiple transfusions and chronic inflammation generating clinically relevant auto and alloantibodies [14]. A delayed hemolytic transfusion reaction (DHTR) and hyper-hemolytic syndrome (HHS) are severe complications that can follow red cell transfusions in SCD patients. Free heme, released beyond the "steady-state" intravascular hemolysis, activates complement, and reduced nitric oxide production and anticoagulant protein, facilitating the hypercoagulation state and the immunological disorder [15]. Our case of severe thrombotic complications in a patient with SS-SCD, who showed high APA levels during vascular occlusions treated also with PE, suggests that APA may contribute directly to the SCD pathophysiology, thus a thrombophilic study including detection of APA in patients with hemoglobin SS disease who developed thrombotic complications after presenting with a severe ischemic stroke should be performed. To date, the prothrombotic role of APA in SCD patients requires further investigation.

Declarations

Ethics approval and consent to participate. This manuscript does not report on or involve the use of any animal or human data or tissue.

Conflict of interest

The authors declare no conflict of interest.

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The effectiveness of an educational session about folic acid on pregnant women's knowledge in Yanbu City, Kingdom of Saudi Arabia

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A B S T R A C T: Background:

Folic Acid (FA) is an important nutritional element during pregnancy. It is B vitamin which is found in the natural and complementary source. Deficiency of FA during pregnancy leads to many maternal and fetal complications such as neural tube defect (NTD), birth defect, spontaneous abortion, and megaloblastic anemia. This study aims to assess the effectiveness of an educational session about FA on pregnant women's knowledge in the Kingdom of Saudi Arabia (KSA). Methods: A quasi-experimental design was conducted on sixty-five pregnant women from the outpatient clinic in Yanbu General Hospital (YGH) using pre-test and post-test questionnaire to assess their FA knowledge. A purposeful sampling method was used to involve the study participants. All the findings were analyzed through SPSS. Descriptive statistic was used to first generate information about the study participants, after which a t-test was conducted. Results: The participants had poor knowledge about FA before the session but the level was increased after the session with mean difference 5.49. Majority of the study participants 81.5% had knowledge that FA protects against NTD. While, 70% understood that FA is an important vitamin during pregnancy. There is a significant association between the age, income, working status, age of marriage, and knowledge of participants. Conclusions: An educational session had good effect on pregnant women's knowledge. Health care providers and social media should play more active role to increase the knowledge of FA to pregnant women.

Keywords: folic acid; educational session; knowledge; pregnant women; Kingdom of Saudi Arabia

1. Introduction

The supplementation of folic acid (FA) benefits the general population and plays a critical role during pregnancy [1]. The World Health Organization (WHO) recommends increasing the nutrition status of women in the first 12 weeks of pregnancy to prevent maternal and fetal adverse outcome [2]. Therefore, mothers should take FA before and during pregnancy to decrease the risks particularly that related to congenital anomalies. According to Kharb et al. [3] and Cieślik et al. [4], FA deficiency leads to various complications in mothers and the fetus, such as spontaneous abortion, megaloblastic anemia, neural tube defect (NTD), and low birth weight. It also affects fetal neurodevelopment and language development. NTD is the most common congenital anomaly in the world with around 300,000 cases a year. Spina bifida is particularly common in Kingdom of Saudi Arabia (KSA), affecting 1.2 in 1000 people [5].

According to the Centers for Disease Control and Prevention (CDC) [6], healthy eating is better complemented by FA supplementations. Pregnant women should not rely on these supplements alone, as they would not meet the amount required to prevent NTDs or other pregnancy-related complications [2]. Therefore, they should eat meals with folate and take vitamins. Additionally, eating fortified foods such as breakfast cereals, cornflour, and bread helps meet the recommended daily folate intake [7]. However, women must combine fortified foods and FA supplements after seeking proper advice from healthcare providers. Moussa et al. [8] and Sonawane et al. [1] emphasized how women's knowledge of FA can reduce the predisposition of complications such as cardiovascular diseases (CVD) and NTDs. Lack of educational knowledge of pregnant women regarding FA intake predisposes them to blood and cardiovascular diseases during and after pregnancy. NTDs are common congenital anomalies that develop within the first month of pregnancy. FA deficiency is a potential predisposing factor to NTDs. Such anomalies lead to anencephaly due to the lack of essential nutrients in the brain for healthy development [9,10].

The level of awareness among women about the effect of FA on lowering congenital problems or cardiovascular risks remains unclear. Sonawane et al. [1] many researcher have argued that the knowledge of supplementation or dosage may be scarce among the patients. The level of awareness of FA supplementation or diet intake during preconception varies from region to region. Alblowi and Alomayri (2018) [11] recommended increasing women's knowledge regarding FA. Consequently, a study that determines the relationship between educational sessions and women's knowledge regarding FA supplementation in KSA will be helpful. The current study thus aims to fill the gap in the literature by assessing the effect of an educational session on the knowledge of pregnant women regarding FA supplementation. The study findings will help the government and relevant healthcare providers predicate required developments to enhance pregnant women's knowledge regarding FA supplementation.

2. Materials and methods

2.1. Study design

In the current study, quantitative, quasi-experimental design was used. It was selected as the proper method that helps to gather insights to reveal the effect of an educational session about FA on Saudi pregnant women's knowledge. In addition, it helps to determine the causal effect of educational sessions on study target population.

Sampling technique involved the selection of the subjects as study samples from the population under study. There are two types of sampling design used in quantitative research: probability sampling and non-probability sampling [12]. In the current study non-probability sampling through purposeful were used. This type of sampling is widely used as it allows the researcher to selects elements through nonrandom methods. The researcher tends to use it when it is impossible to draw random probability sampling due to time or cost considerations. A purposeful sampling requires the researcher to examine the study population to ensure that they fit the purpose of the study in order to measure what is suppose to measure.

2.2. Study site

This study was conducted in antenatal clinic at Yanbu General Hospital (YGH) from February 2021 to May 2021. YGH is a governmental hospital located in Yanbu City which is a small and beautiful city located in the Western provenance of KSA.

2.3. Study sample

The sample size was a total of 65 pregnant women. A purposeful sampling method was used to include the study participants. The inclusion criteria include: (a) Saudi pregnant women; (b) age 18–45 years; (c) living in Yanbu City; (d) ability to speak Arabic. The exclusion criteria include: (a) nonSaudi pregnant women; (b) age < 18 or > 45 years; (c) living outside the Yanbu City.

2.4. Instrument

The instrument of this study was developed by the researchers concerning the comprehensive reading of the literature, and it was then revised by two academic professors specialized in maternity health nursing in the Nursing Faculty at King Abdulaziz University (KAU). The reliability tested by using Cronbach's Alpha (α) test using the IBM-SPSS package. The technique confirmed that the scales used in the survey items are reliable. The data was collected using a questionnaire divided into three parts: (1) Demographic data and obstetric history; (2) Knowledge about FA before and after the session, this part was same and administered twice before and after the educational session; (3) Satisfaction about the educational session which conducted one time only immediately after the educational session.

The study intervention was made through an educational session related to FA provided by one of the researcher. The educational session was developed by the researchers. The objective of the educational session is to provide knowledge related to FA. The educational session includes information about the importance of FA, complication related to not using FA, the advantages of taking FA on women and child health. The session was provided for each participant through a PowerPoint presented by the researcher at the antenatal clinic, and the duration of the session was 10–15 min.

2.5. Data collection process

In quantitative studies, the researcher explains how to operationalize their variables and collect their data. Their data collection plan is usually before a single piece of data is gathered. The researcher must transfer the phenomena that interested into data that can be analyzed through the data collection stage. The researcher visited the clinic daily for data collection. The sample subjects included those who visited the waiting area of the antenatal clinic at YGH. The researcher introduced herself and explained the title, aims, and study objectives to each of the participants to obtain their consent for participation.

Pre-test questionnaires were filled by the researcher based on the interview with each participant individually. Then, the researcher provided the educational session. At the end of the educational session, the participants were asked to evaluate the session presented to them. For this purpose, the participants who could read and write were left alone and asked to fill the feedback form.While those who couldn't, they filled the evaluation by the help of the relatives or nurse or attending visitors available in the clinic. After two weeks, the researcher contacted each participant through telephone to collect their

post-test answers by reading the question and fill the questionnaires. Evaluating the impact of education after two weeks was suitable in this study as it help to follow up with the study participants and not losing the contact data.

2.6. Data analysis

All data were coded, computed, and analyzed using the Statistical Package for Social Science (SPSS; version 25). The researcher started by reviewing the data obtained (i.e., eliminating missing data and outliers). Descriptive statistic was used to first generate information about the study participants, after which a t-test was conducted to determine if there is a significant difference between the means of two groups. In addition, Tukey hoc test is used with one way ANOVA and when the P value significant difference between the means of two groups, which may be related in certain features. It is considered the best available method when confidence intervals are desired. Coding refers to a numerical or textual label implemented to a section of raw data to facilitate subsequent analyses. The researcher prepared codes to depict categories of subject or rank order placement. A coding system was developed to convert the verbal data into numbers.

2.7. Ethical considerations

The research proposal for this study was first approved by the Ethical Committee of the Nursing Faculty at KAU (Ref. No. 1M.10) and then by the ethical committee in Ministry of Health (MOH) in Madinah (IRB 555) to facilitate access to the participants and to gather the necessary data. The researcher was cleared that the participation in the study is voluntary and they can withdraw at any time or stage during the study. The participant's privacy and confidentiality of their personal information were well maintained. The data were anonymized and protected from unauthorized parties.

3. Results

3.1. Sample distribution according to the participants' age, marital status, income, residence, education, working status, age at marriage, and age at first delivery

Table 1 shows the distribution of study participants according to their age groups, their hus bands' age, marital status, income, and their residence. Women aged 26–30 years old constitute 30.8%, while, 26.2% of them are aged between 18–25 and 16.9% of them are from 36–45 years old. In addition, the age of 40.0% of the participants' husbands is >36 years old, while the age of 24.6% of participants' husbands is 26–30 years. The majority 90.8% of the participants are married, while 9.2% are separated or divorced. Regarding their income, 40.0% of the participants have an income between 3000–6000 SAR, 36.9% of them have an income between 7000–9000 SAR, while 23.1% have an income >9000 SAR. The majority of the samples, 86.2%, are from the West, while 6.2% of them originate from the North.

The participants' educational qualifications 49.2% of the participants have a University degree, 24.6% of them are Illiterate, while 23.1% have a secondary school education. Regarding their husbands' educational qualifications, the majority of them, 49.2%, have a secondary school education, while 46.2% of them have a University degree. In addition, more than half, 53.8%, of the participants are housewives, while 30.8% are working. Furthermore, 87.7% of the participants' husbands are working, while 12.3% of them are not working. Regarding the participants' age at marriage, 50.8% of them were

married when their age was less than 20 years, while 26.2% were married after the age of 25. On the other hand, the age at the first delivery of 38.5% of the participants was 20 years or less, and that of 33.8% of participants was 21–25 years.

Table 1. Sample distribution according to the participants' age, marital status, income, residence, education, working status, age at marriage, and age at first delivery.

Variables	Number (n)	Percentage (%)
Participant's age groups		
18–25 years	17	26.2
26–30 years	20	30.8
31–35 years	17	26.2
36–45 years	11	16.9
Husband's age groups		
18–25 years	3	4.6
26–30 years	16	24.6
31–35 years	20	30.8
More than 36 years	26	40.0
Marital status		
Married	59	90.8
Separated/Divorced	6	9.2
Income		
3000–6000 SAR	26	40.0
7000–9000 SAR	15	23.1
> 9000 SAR	24	36.9
Residence		
North	4	6.2
South	3	4.6
East	2	3.1
West	56	86.2
Participants' education		
Read and Speak Arabic	16	24.6
Secondary	15	23.1
University	32	49.2
Others	2	3.1
Husbands' education		
Intermediate	3	4.6
Secondary	32	49.2
University	30	46.2
Participants' working status		
Housewife	35	53.8
Student	10	15.4
Working	20	30.8
Husbands' working status		
Not working/Retired	8	12.3
Working	57	87.7
Age at marriage		
Less than 20 years old	33	50.8
21–25 years	15	23.1
More than 25 years	17	26.2
Age at first delivery		
Less than 20 years old	25	38.5
21–25 years	22	33.8
More than 25 years	18	27.7

3.2. Sample distribution according to the participants' history of diseases, previous operations, planning for current pregnancy, and nature of current pregnancy

Table 2 below shows that majority of the participants 67.7% did not have any history of diseases, 23.1% had anemia, while 4.6% had diabetes mellitus. Furthermore, 70.8% of the participants did not have any previous operations, 12.3% of them had a Cesarean Section (CS), while 7.7% of them had a cholecystectomy. Regarding planning for the current pregnancy, more than half, 52.3%, of the participants had a plan for a pregnancy, while 47.7% did not. Moreover, all participants had spontaneous pregnancies.

Table 2. Sample distribution according to the participants' history of diseases, previous operations, planning for current pregnancy, and nature of current pregnancy.

Variables	Number	Percentage (%)
History of medical diseases		
No history of diseases	44	67.7
Anemia	15	23.1
Obesity	1	1.5
Diabetes mellitus	3	4.6
Hypertension	1	1.5
Others	1	1.5
History of previous operations		
No	46	70.8
Appendectomy	4	6.2
Cholecystectomy	5	7.7
Cesarean section	8	12.3
Others	2	3.1
Planning for current pregnancy		
Yes	34	52.3
No	31	47.7

3.3. Sample distribution according to their obstetric history

Table 3 shows that the gestational age of 64.6% of participants is 1–3 months, and the gestational age of 23.1% of them is 4–6 months. Regarding gravida, 76.9% of the participants had 1–3 pregnancies, while 23.1% of them had 4–6 pregnancies. Regarding the number of previous deliveries, 50.8% of the participants had 1–3 deliveries, while 26.2% of them did not have any delivery. In addition, 60.0% of the participants had previous normal vaginal delivery, while 1.8% of them had previous CS delivery. Regarding the number of alive children, 44.6% of the participants had 1–3 children, 38.5% of them did not have children, while 16.9% had 4–6 children. In addition, the majority, 93.8%, of the participants did not have congenital anomalies for their previous births. Moreover, the time difference between the current and last pregnancy of 32.3% of the participants is 2–4 years, while the time difference of 30.8% of the participants is less than 2 years. 27.7% of the participants were pregnant for the first time.

Table 3. Sample distribution according to their obstetric history.

Variables	Number (n)	Percentage (%)
Gestational age		
1–3 months	42	64.6
4–6 months	15	23.1
7–9 months	8	12.3
Number of pregnancy		
1–3 pregnancies	50	76.9
4–6 pregnancies	15	23.1
Number of delivery		
0 deliveries	17	26.2
1–3 deliveries	33	50.8
4–6 deliveries	15	23.1
Abortion		
0 times	43	66.2
1–3 times	22	33.8
Mode of previous deliveries		
No previous deliveries	17	26.2
Normal vaginal delivery	39	60.0
CS	9	13.8
Mode of last delivery		
No previous deliveries	17	26.2
Normal vaginal delivery	38	58.5
CS	10	15.4
Number of alive children		
0	25	38.5
1–3	29	44.6
4–6	11	16.9
Previous congenital anomalies		
No	61	93.8
Yes	4	6.2
Time difference between current and last pregnancy		
Pregnant for the first time	18	27.7
Less than 2 years	20	30.8
2–4 years	21	32.3
More than 3 years	6	9.2

3.4. Participants' knowledge about FA before and after the educational session

Table 4 shows the frequency and percentages of correct and incorrect answers of each item within the participants' knowledge about FA before and after intervention. Majority of the participants 81.5% had correct answers about the item "FA during pregnancy protects against malformations of the fetus's nervous system", 70.0% had correct answers about the item "FA is one of the important vitamins during pregnancy", and 60.0% had correct answers about "FA promotes the health of the mother and the fetus during pregnancy". On the other hand, 84.6% of the participants had incorrect answers about the item "The appropriate dose of FA for a pregnant woman who does not suffer from diseases is 800 micrograms", 75.4% of them had incorrect answers about the item "Natural sources of FA only are sufficient to get the right dose during pregnancy", and 73.8% of them had incorrect answers about the

item "The appropriate daily dose of FA for a non-disease-free pregnant woman is 400 micrograms".

Table 4. Participants' knowledge about FA before and after the educational session.

Knowledge statements	Before session		After session	
	Correct answer n (%)	Incorrect answer n (%)	Correct answer n (%)	Incorrect answer n (%)
1. FA is one of the important vitamins during pregnancy.	46 (70.8)	19 (29.2)	61 (93.8)	4 (6.2)
2. FA is an important mineral during pregnancy.	36 (55.4)	29 (44.6)	55 (84.6)	10 (15.4)
3. FA helps in iron absorption.	36 (55.4)	29 (44.6)	62 (95.4)	3 (4.6)
4. FA protects against early miscarriage.	31 (47.7)	34 (52.3)	64 (98.5)	1 (1.5)
5. FA protects against depression and promotes mental health.	31 (47.7)	34 (52.3)	65 (100.0)	0 (0.0)
6. FA during pregnancy protects against malformations of the fetus' nervous system.	53 (81.5)	12 (18.5)	64 (98.5)	1 (1.5)
7. FA promotes the health of the mother and the fetus during pregnancy.	39 (60.0)	26 (40.0)	61 (93.8)	4 (6.2)
8. One of the sources of FA is beans.	34 (52.3)	31 (47.7)	63 (96.9)	2 (3.1)
9. One of the sources of FA is orange.	29 (44.6)	36 (55.4)	61 (93.8)	4 (6.2)
10. One of the sources of FA is green leaves, such as watercress.	36 (55.4)	29 (44.6)	65 (100.0)	0 (0.0)
11. One of the sources of FA is corn.	27 (41.5)	38 (58.5)	61 (93.8)	4 (6.2)
12. Avocado is one of the sources of folate.	29 (44.6)	36 (55.4)	62 (95.4)	3 (4.6)
13. Banana is one of the sources of folate.	28 (43.1)	37 (56.9)	61 (93.8)	4 (6.2)
14. Pomegranate is considered a source of FA.	28 (43.1)	37 (56.9)	62 (95.4)	3 (4.6)
15. FA should be taken at least three months before planning a pregnancy	25 (38.5)	40 (61.5)	62 (95.4)	3 (4.6)
16. FA should be taken three months after pregnancy.	23 (35.4)	42 (64.6)	63 (96.9)	2 (3.1)
17. A pregnant woman needs a dose of FA that differs from the dose of a non-pregnant woman.	21 (32.3)	44 (67.7)	64 (98.5)	1 (1.5)
18. The appropriate dose of FA for a pregnant woman who does not suffer from diseases is 800 micrograms.	10 (15.4)	55 (84.6)	62 (95.4)	3 (4.6)
19. The appropriate daily dose of FA for a non-disease-free pregnant woman is 400 micrograms.	17 (26.2)	48 (73.8)	63 (96.9)	2 (3.1)
20. Natural sources of FA only are sufficient to get the right dose during pregnancy.	16 (24.6)	49 (75.4)	65 (100.0)	0 (0.0)
21. Nutritional supplements only are sufficient to get the right dose during pregnancy.	34 (52.3)	31 (47.7)	62 (95.4)	3 (4.6)
22. It is safe to buy FA without a prescription.	34 (52.3)	31 (47.7)	64 (98.5)	1 (1.5)

Frequency and percentages of the correct and incorrect answers of each item within the participants' knowledge about FA after the intervention changed. It shows that all participants had correct answers about the item "One of the sources of FA is green leaves, such as watercress", 98.5% had correct answers about the item "It is safe to buy FA without a prescription", "FA protects against early miscarriage", and "FA during pregnancy protects against malformations of the fetus' nervous system". On the other hand, all participants had correct answers about the item "Natural sources of FA only are sufficient to get the right dose during pregnancy", 98.5% of them had correct answers about the item "A pregnant woman needs a dose of FA that differs from the dose of a non-pregnant woman", and 96.9% of them had correct answers about the item "FA should be taken three months after pregnancy".

3.5. Total knowledge before and after the educational session

Table 5 below shows that 44.6% of participants had poor knowledge about FA before the intervention, while no participants had a poor level of knowledge after the educational intervention, Moreover, the percentage of participants having excellent knowledge after the educational intervention increased from 30.8% to 92.3% after the intervention.

In addition, the percentage of participants having adequate knowledge after the educational intervention decreased from 24.6% before the intervention to 7.7% after the intervention. The table also shows that the educational intervention about FA during pregnancy has a significant effect on the participants' level of knowledge. The mean of the participants' knowledge about FA after the intervention is significantly higher than the mean of it before the intervention ($p < 0.001$).

Table 5. Total knowledge before and after the educational session.

Level of knowledge	Before (%)	After (%)
Poor (< 40.0%)	29 (44.6)	0 (0.0)
Adequate (40–60%)	16 (24.6)	5 (7.7)
Excellent (> 60.0%)	20 (30.8)	60 (92.3)
Total	65 (100.0)	65 (100.0)

Knowledge about FA before and after the educational session					
FA knowledge before and after	N	Mean difference	SD difference	T (df)	P-value*
	65	–5.49	5.34	–8.285 (64)	0.000

3.6. Sources, time and benefits of information regarding FA

Table 6 below shows the sources of information, time, and benefit regarding FA among the study participants. The most common source of information used by them was physicians (58.2%). It was followed by social media (46.2%) and then nurses (6.2%), while the health education program and newspapers accounted for 0.0%. (84.6%) of the participants stated that they had information about FA before marriage, while less than one-fourth (15.4%) did not had any information. In addition, more than half (53.8%) of the participants did not agree with "My prior knowledge of FA helped me to take the dose at the right time during pregnancy", while less than half (46.2%) mentioned it did.

Table 6. Sources, time and benefits of information regarding FA.

	Question answer	Frequency	%
Source of information			
Social media	Yes	30	46.2
	No	35	53.8
Health education program	No	65	100.0
Physicians	Yes	38	58.5
	No	27	41.5
Nurses	Yes	4	6.2
	No	61	93.8

Family	Yes	25	38.5
	No	40	61.5
Newspaper	No	65	100.0
Others	Yes	4	6.2
	No	61	93.8
Time of information			
Got information about FA well before pregnancy	Yes	10	15.4
	No	55	84.6
Benefits of information about FA			
My prior knowledge of FA helped me to take the dose at the right time during pregnancy	Yes	30	46.2
	No	35	53.8

3.7. Differences in the participants' knowledge of FA before the educational session with regard to their age, marital status, income, and residence

Table 7 below shows that there is a significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their age groups ($p < 0.05$). The Tukey post hoc test showed that the difference is between the age group 18–25 years and 31–35 years in favor to participants who are 31–35 years. The participants who are aged 31–35 years had a significantly higher mean knowledge score than the participants aged 18–25. In addition, there is a significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their income ($p < 0.05$). The Tukey post hoc test showed that participants who have an income > 9000 SAR had significantly higher mean knowledge scores than those who have an income between 7000–9000 SAR. On the other hand, there is no significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their marital status, husbands' age, and residence ($p > 0.05$).

Table 7. Differences in the participants' knowledge of FA before the educational session with regard to their age, marital status, income, and residence.

Total level of knowledge before the educational session	N	Mean	SD	F/t (df)	P-value*
Age groups					
18–25 years	17	7.76	5.36	3.439 (3, 61)	0.022[a]
26–30 years	20	10.85	5.08		
31–35 years	17	12.94	5.56		
36–45 years	11	8.54	3.64		
Marital status					
Married	59	9.949	5.40	–1.184 (63)	0.241[b]
Separated/divorced	6	12.66	4.67		
Husband's age					
18–25 years	3	8.66	1.52	1.120 (3, 61)	0.156[a]
26–30 years	16	8.50	6.12		
31–35 years	20	12.35	4.29		
≥ 36 years	26	9.76	5.58		

Income					
3000–6000	26	9.30	4.71	3.918 (2, 62)	0.025[a]
7000–9000	15	8.13	5.78		
> 9000 SAR	24	12.45	5.17		
Residence					
North	4	9.50	6.45	0.352 (3, 61)	0.788[a]
South	3	10.66	5.50		
East	2	6.50	2.12		
West	56	10.35	5.43		

3.8. Differences in the participants' knowledge of FA before the educational session with regard to their education, working status, age at marriage, and age at first delivery

Table 8 below shows that there is a significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their working status ($p < 0.05$). The Tukey post hoc test showed that the difference is between working women and housewives in favor to working women. The participants who are working had significantly higher mean knowledge scores than housewives.

In addition, there is a significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their age at marriage ($p < 0.05$). The LSD post hoc test showed that the difference is between the participants who have been married at ≤20 years old and those who have been married at age of >25 years old in favor to participants who have been married at age >25 years. The participants who had been married at the age >25 years had significantly higher mean knowledge scores than those who had been married at ≤20 years. On the other hand, there is no significant difference in the mean level of the total participants' knowledge regarding FA during pregnancy with regard to their education, husbands' education, husbands' working status, age at first delivery, and planning for current pregnancy ($p > 0.05$).

Table 8. Differences in the participants' knowledge of FA before the educational session with regard to their education, working status, age at marriage, and age at first delivery.

Total Level of Knowledge before the educational session	N	Mean	SD	F/t (df)	P-value*
Participants' education					
Illiterate	16	8.50	4.00	1.999 (3, 61)	0.123[a]
Secondary	15	8.60	5.85		
University	32	11.62	5.56		
Others	2	13.00	1.41		
Husbands' education					
Intermediate	3	8.33	4.16	2.279 (2, 62)	0.111[a]
Secondary	32	8.96	4.61		
University	30	11.70	5.94		

Participants' working status					
Housewife	35	9.11	4.15	8.633 (2, 62)	0.000[a]
Student	10	6.90	5.83		
Working	20	13.75	5.37		
Husbands' working status					
Not working/Retired	8	12.62	2.77	1.373 (63)	0.175[b]
Working	57	9.85	5.57		
Age at marriage					
≤ 20 years old	33	8.45	4.86	3.858 (2, 62)	0.026[a]
21–25 years	15	11.93	5.63		
> 25 years	17	12.05	5.23		
Age at first delivery					
≤ 20 years old	25	8.72	5.18	2.480 (2, 62)	0.092[a]
21–25 years	22	10.13	5.35		
> 25 years	18	12.33	5.21		
Planning for current pregnancy					
Yes	34	9.35	5.47	−1.340 (63)	0.185[b]
No	31	11.12	5.18		

3.9. Participant satisfaction with the educational session

Table 9 is the evaluation of the educational session that was given to participants about FA. All study participants satisfied from the educational session provided to them. 100.0% of participants benefited from the educational session that was presented to them about FA, 100.0% of them said that the educational session is sufficient in terms of time, 100.0% of them were satisfied with the educational session given, 100.0% of them said that the educational session helped them make sure to take FA, and 100.0% of them said that the educational session provided them with information that they did not previously know about FA.

Table 9. Participant satisfaction with the educational session.

Educational session evaluation	Yes (%)	No (%)
1. I benefited from the educational session that was presented to me about FA.	65 (100.0)	0 (0.0)
2. The educational session is sufficient in terms of content.	53 (81.5)	12 (18.5)
3. The educational session is sufficient in terms of time.	65 (100.0)	0 (0.0)
4. Overall, satisfied with the educational session given.	65 (100.0)	0 (0.0)
5. The educational session helped me make sure to take FA.	65 (100.0)	0 (0.0)
6. The educational session provided me with information that I did not previously know about FA.	65 (100.0)	0 (0.0)

4. Discussion

The present data shows that the majority of the study sample had poor total score of knowledge about FA before the educational session 44.6%. The results are consistent with the findings of national and

international studies about FA. The finding aligns with the views of Nemri et al. (2019) [13] that 45.7% of pregnant women queried in the study lacked the fundamental knowledge about FA. The finding also in line with a questionnaire-based cross-sectional study in Riyadh, KSA involved two hundred and fifty four Saudi pregnant women and has reported that only 51.4% of the women in their study gave the correct reason for taking FA [10]. A study by Alreshidi et al. (2018) [14] have concluded that there is a distinct need to increase the level of Saudi women's awareness of the importance of taking FA in the preconception period. In contrary, a Saudi study conducted in Hail city found that majority 91.0% of the subjects were aware of FA [15]. There are possible reasons for finding poor knowledge about FA in the current study. The current study conducted in Yanbu which is a small city with relatively low health resources. Decease in health care services can have impact on the quality of services provided to women in hospital such as antenatal education and counselling which consequently inhibit women's awareness about FA. The current study revealed that the highest knowledge score was observed among the age group of 31–35, have income more than 9000, working and marriage at age of 25 or above. It can conclude that age, income, working status and age at marriage are all influence factors helped to increase the women's knowledge about FA. Women with high income are probably more able to take care of their health by frequent visiting to maternity clinic and ability to buy FA. While women aged 31–35 and marriage at age 25 or above may have pregnancy experience which increase their knowledge about FA. Al-Holy et al. (2013) [15] agree that the women aged from 26–35 years with income more than 5000 and working status helped to increase the knowledge of FA. Despite the fact that the current study participants had lower score for total knowledge about FA, however, they get high score in specific statements. It is worth to mention that more than half of the study sample 70.8% understood that FA is an important vitamin during pregnancy. The result aligns with international study conducted by Jamil et al. (2017) [16] found that 54% know about the importance of FA during pregnancy.

In addition, the present data shows that the majority of participants understood FA's role in preventing malformation of the fetus's nervous system. These findings agree with the results of Al-Ahmadi et al. (2014) [17] who conducted the study in Makkah, KSA and found that more than half of participants knew that FA prevents NTD. Another cross-sectional study conducted at King Fahad Medical City in Riyadh, KSA also found that 80.1% (n = 480) of women were aware that it isused to prevent NTDs [14]. On the other hand, Kari et al. (2008) [18] conducted a national study between students in the college found a different result, that 88% of students didn't understand the importance of FA in preventing NTD during pregnancy. The student was in reproductive age between 20–25 years old and study was done in 2008 which may a reason of differences with the current study finding. There was also a study conducted in Egypt by Al-Darzi et al. (2014) [19] observed opposite result with current study, they reported that only 39.2% of the study sample had knowledge about the importance of FA in preventing NTD. Regarding the knowledge about the correct dose of FA for pregnant women, the current study revealed that the majority of participants don't have knowledge about the correct dose of FA. Similarly, Kamran et al. (2018) [20] have reported that most women in their study did not know about FA dose. On the other hand, Alreshidi et al. (2018) [14] conducted study in King Fahad Medical City, Riyadh found different results, 84.3 % of women in their study know about FA dose. They conclude that greater awareness of the importance of FA, was attributed to better education for their study sample.The present study shows that 61.5% had an incorrect answer about the knowledge of the proper time of FA intake. The findings are consistent with national study conducted by AbdRabou (2019) [21] who found that 69.6 % of women in Sakaka, KSA did not understand the right time of FA intake. However, no relation between knowledge and education level of the participants was found.

On the other hand, another study was conducted in Tabuk, KSA by Alblowi and Alomayri (2018) [11] had different results. They reported that most participants had knowledge about using FA three months before pregnancy and first trimester of pregnancy. Although, the current study did not found significant relation between knowledge and participants educational level, however, many studies have reported that educated women had significantly better knowledge about FA. A Saudi study conducted in Hail reported that participants who were postgraduates have a significantly better knowledge regarding FA [22] Another study was conducted in Sudan found that the educated women had very good knowledge about FA [23] In their study, they reported that the women who were educated have advantages, lived in the urban country and visiting antennal clinic which is a reason for having more knowledge about FA than others. In the current study, the health education sessions affected participant's knowledge about FA positively. Majority of the study participants 92.3% had an excellent knowledge after the educational session. The increment in the knowledge of FA after education aligns with national and global studies, conducted by Alodan and Ghoraba (2018) [24] who reported improvement of participant's knowledge, they found that more than half of participants had very good knowledge 80% about FA after education sessions at Security Forces Hospital, Saudi Arabia. In addition, De Smit et al. (2015) [25] have established the value of the educational sessions in reducing the abnormalities or the extreme health implications with limited or zero intakes of FA after Dutch pregnant women received the knowledge during well-baby clinics (WBCs) to enhance the preconception intake of FA. It was argued that the way of presenting the information about FA through PowerPoint individually gave the participants the opportunity to understand the importance of FA during Pregnancy [26].

The current study also revealed that the educational session enhanced the participant's knowledge of specific statements which were incorrect before the educational session. Most of the current study samples were aware of the dose of FA after the session. Similar results were found by Kari et al. [18], they found that the level of awareness about the correct dose of FA increased after education lecturers. Varies methods used by the health care providers such as Lectures, health programs, text messages, or poster have helped the women to know about FA dose and motivate them to use it during pregnancy.In the current study most of the study sample had knowledge about the appropriate time of FA using three months before pregnancy after the educational session. A similar study conducted by De Smit et al. (2015) [25] found an increase in the knowledge about FA intake 3 months before pregnancy this improvement was noted after the educational session presented to them. The evidence from the current study shows that physician is the most reported source of knowledge about FA to pregnant women who seeking antenatal care. The results are congruent with findings of Al Essa et al. (2019) [27] when they studied 297 pregnant women at King Abdulaziz Medical City, Riyadh and found increased reliance on healthcare professionals. Other study conducted in Jeddah, KSA by Balkhair et al. (2019) [28] found also that doctor are the primary source of information about FA intake. Physicians are reliable sources of education and guidance needed to prevent complications during pregnancy. The results were also evident in another study by Al-Ahmadi (2014) [17] concurred with the results of the present study on Saudi women using informational sources such as physicians, internet, and media.

The social media was the second source in the current study, documented similar findings where the participants derive the information from social media platforms such as blogs, websites, Facebook, Twitter, YouTube, and Instagram. The results differed with the outcomes of Al-Hakeem (2012) [29] who established internet as among other informational sources for the 4000 women studied in King Khalid University Hospital, Riyadh, KSA. Agreeably, Yamamoto and Wada (2018) [30] considered the social media platforms and mass campaigns as interactive media that led to 20.5% of periconceptional FA

intake. Therefore, different educational sources including social media and public health programs shape intake of FA by promoting behavioral changes among women of reproductive age. The present study shows that family is the third source of FA insights for the study sample. The results show that pregnant women and those planning pregnancies rely on family to complement education from social media, mass campaigns, and interactive media. The outcomes were congruent with Alodan and Ghoraba (2018) [24] who had maternal knowledge after seeking informational sources from the antenatal in 80% of the pregnant women. The sources then shaped the intake of FA in the first 3 months and during pregnancy. Correspondingly, Kannan et al. (2020) [31] emphasized the importance of family as the source of education on FA when they analyzed the grocery store campaign in Michigan. Family is a free and convenient source of insights on dosage and nutritional modification to enhance fortification. Saudi community is featuring of extended family, and still with its strong ties. Family usually gathered with each other daily or weekly and during their gathering they talk about life, health, and other topics. In addition, due to cultural norm, women during postpartum period stayed at their family home and welcoming visitor from family and friends for around 40 days which is an opportunity for sharing experience and providing advice [32].

Sadly, the present study revealed that nurses 6.4% have limited role in educating pregnant women about the importance of FA during pregnancy. Other national studies agree with this finding [33]. They found that the nurse were the lowest source of information about FA. The role of the nurses in some hospitals is limited because these hospitals restrict the nurses from providing antenatal education to patients, as they may believe this is the doctor's role. Taking in account that there is a shortage in nursing staff in KSA and nurses are strictly allocated for clinical patients care particularly during COVID-19 pandemic. Mostly at antenatal clinics in KSA, the nurse's role was limited by receiving the patients, taking vital signs and prepares them for doctor examination. In addition, most nurses in KSA are non-Arabic speakers, which affects their participation in education due to the language barrier. However, in contrast to current study, Adebo et al. (2017) [34] conducted a study in Nigeria found that a major source of FA was health care provider including nurses. Also a study conducted in KSA found that nurses' play an active roles in postpartum education [35]. The WHO have clearly emphasized about the importance of empowering nurses, advocating for expanded the roles of nurses, and increasing the investments in the nursing workforce [36]. Nurses can make significant differences in the public health in terms of prevention of disease and promotion of health.

5. Conclusions

FA before and during pregnancy is important because it help in preventing various maternal and fetal complication. Women awareness about FA can influence its intake. This study concludes that knowledge level about FA increased after providing an educational session. The role of Healthcare institutions and antenatal clinics should be effective by sensitizing pregnant mothers on the different sources of FA to increase their knowledge of the vitamins and should invest in educational initiatives through mass media options such as text messaging and broadcast. Also, the role of Hospitals is very important through investment in training programs presided by the nurses and physicians. Understanding the value of FA in preventing maternal and fetal complication can lead to enhancing women health. Therefore, training sessions within the healthcare institutions and communities should teach and empower pregnant mothers on the different intake of FA. The health care professional should provide educational sessions to emphasize the importance of taking FA to women, particularly during their premarital stage and antenatal visit. In addition, the Saudi government through the MOH should enhance women's

knowledge about FA supplementation and diets through media, schools and universities, antenatal class, routine antenatal care, family planning clinics.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki. The research was reviewed and approved by the ethical committee of the Faculty of Nursing at King Abdulazaiz University (Ref. No. 1M.10).

Informed consent statement

Informed consent was obtained from all study participants involved in the study.

Authors' contributions

Conceptualization: AAZ; data curation: SAM; formal analysis: SAM; methodology: AAZ and SAM; supervision: AAZ; writing original draft: AAZ and SAM; writing, review and editing: AAZ and SAM.

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Conflict of interest

The authors declare no conflict of interest.

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Cytokine profile and oxidative stress parameters in women with initial manifestations of pelvic venous insufficiency

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A B S T R A C T: Background:

Pelvic venous insufficiency (PVI) in women is widespread and is closely associated with the risk of reproductive disorders (in 15–25% of patients) and a high rate of the disease recurrence after treatment. The factors involved in venous wall damage include atherogenic stimuli and chronic endotoxin aggression due to inflammatory processes. The changes in the initial stages of the disease are usually minor and selective. There is currently an urgent need to identify initial markers of these changes to develop preventive measures for their correction. Therefore, the aim of this study was to determine the cytokine profile parameters' levels, as well as the activity of lipid peroxidation (LPO) and antioxidant defense (AOD) reactions in women with initial manifestations of PVI. Thirty-nine female patients with PVI (mean age 37.4 ± 9.1 years old) were the subjects of the study. The diagnosis was verified by clinical and instrumental examination including ultrasound angioscanning of the pelvic veins and therapeutic and diagnostic laparoscopy, and it was finally confirmed histologically. The control group included 30 nearly healthy women (mean age 33.5 ± 6.3 years old) who underwent surgical sterilization by laparoscopic access. Spectrophotometric, fluorometric and immunoassay methods were used in the study. The cytokine profile in female patients with PVI, as compared to the control group, was characterized by an increased concentration of proinflammatory (interleukin (IL) (IL-6) and IL-8) and anti-inflammatory cytokines (IL-4 and IL-10) and higher ratio values (IL-6/IL-10). The level of primary LPO products, conjugated dienes, was significantly increased and level of final products TBARs values was decreased in comparison to the control. The AOD system main enzyme activity, superoxide dismutase (SOD), was decreased, while the catalase activity increased. In patients with PVI, the glutathione reduced form concentration was lower than in the control group. The results of the study in women with PVI suggest negative changes in the cytokine profile and multidirectional changes in the indicators of the LPO system state in the initial stages of the disease. The control of these changes in patients with PVI should probably be an important component of preventive measures in the initial stages of the disease.

Keywords: inflammation; lipid peroxidation; antioxidant defense; pelvic venous insufficiency

Abbreviations:

PVI: Pelvic venous insufficiency; LPO: Lipid peroxidation; AOD: Antioxidant defense; TNF: Tumor necrosis factor-alpha; IL: Interleukin; LH: Lipid hydroperoxides; Cds: Conjugated dienes; TBARs:

Thiobarbituric acid reactants; SOD: Superoxide dismutase; GSH: Reduced glutathione; GR: Glutathione reductase; GPO: Glutathione peroxidase; G-S-T: Glutathione-S-transferase; SEM: Standard error of the mean

1. Introduction

Pelvic venous insufficiency (PVI) in women is widespread and is closely associated with the risk of reproductive disorders (15–25% of patients) and a high rate of the disease recurrence after treatment [1]. There are hemodynamic disorders, pelvic varicose vein transformation, the presence of chronic pelvic pain and bleeding in this disease. The risk factors of the disease include heredity, gender, age, professional activity, sedentary lifestyle, multiple pregnancies and bad habits [2]. The main defect in PVI is reflux through incompetent ovarian and pelvic vein valves [3,4]. Until now, there are no clear ideas about the mechanisms that lead to valve failure. On the one hand, it can be primary changes in the valve structure that lead to their leakiness and progression of reflux [5]. On the other hand, there can be structural abnormalities in the vein wall, leading to their dilation and, consequently, to valve deformation [4,6]. Regardless of the triggering events, prolonged venous dilatation causes inflammation, which destroys the valve structure further, leading to significant reflux [6]. It is known that endothelial cells are a key link in the chain of reactions of venous wall remodeling. It is known they encounter first to the free radicals, oxidized low-density lipoproteins, chemical agents [7]. An important role is assigned to various biosubstrates, free-radical oxidation, in particular to lipid peroxidation (LPO)-antioxidant defense (AOD) processes [8–11]. It was established that the free radicals' biological effects are realized both through their direct effects on proteins, amino groups, phospholipids and nucleic acids and through LPO products of the chain reaction [12]. Biomembrane deformation, ion transport dynamics changes, enzyme activity changes and other pathological phenomena are possible [12,13].

The factors involved in endothelial damage include atherogenic stimuli and chronic endotoxin aggression due to inflammation [14]. All these factors lead to vascular endothelial damage and dysfunction development. Endothelial dysfunction is understood as an imbalance between production of vasodilative, angioprotective and antiproliferative factors, on the one hand, and vasoconstrictor, prothrombic and proliferative endothelial progenitors, on the other [6,7,15]. Endothelial changes in initial the disease stages are usually minor and selective. At the same time, there is an urgent need to identify initial markers of these changes, which will allow to take initial preventive measures for their correction. There are still insufficient data on cytokine profile changes and nonspecific lipid peroxidation system activity in the PVI initial stages. Presented by these studies mechanisms of LPO influence on varicose veins formation is fragmentary and does not reflect their association with inflammatory reactions [13,16]. Therefore, the aim of this study was to determine the level of cytokine profile parameters, as well as the activity of lipid peroxidation and antioxidant defense reactions in women with PVI initial manifestations.

2. Materials and methods

2.1. Design of study

The subjects were 39 patients with PVI (mean age 37.4 ± 9.1 years old). The diagnosis was verified by clinical and instrumental examination and included pelvic veins ultrasound angioscanning and

therapeutic and diagnostic laparoscopy, and it was finally confirmed histologically [17]. The control group included 30 healthy women (mean age 33.5 ± 6.3 years old) who underwent surgical sterilization with laparoscopic access.

Inclusion criteria were as follows: female; reproductive age; primary PVI confirmed diagnosis by ultrasound examination with duplex angioscanning; absence of concomitant gynecological pathology, gynecological diseases and organic lesions in the pelvis; informed consent to participate in the study. Exclusion criteria were the following: acute gynecological and somatic pathology; oncological diseases; history of pelvic surgeries (not earlier than 6 months); postpartum period (less than 6 months); varicose veins of the lower extremities at the time of study inclusion; refusal to participate in the study. Inclusion criteria for the control group were as follows: female, reproductive age, absence of acute disease or exacerbation of chronic diseases at the time of the study, absence of pathology of the venous system.

Exclusion criteria for both groups: pregnancy, intake of venotonics, angioprotective drugs, antioxidant drugs or synthetic analogues of female sex hormones (hormonal contraceptives) during the last 6 months.

2.2. Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia (protocol No. 3.1 and date of approval 26 October 2012).

2.3. Instrumental measurements

The pelvic varicose veins assessment was performed on a Voluson (GE10 Healthcare, Austria) using a 4–8 MHz convex transducer and 7 MHz vaginal transducer. The ultrasound criterion for PVI was pelvic venous plexus ectasia over 5 mm combined with retrograde blood flow lasting more than 0.5 s recorded during Valsalva test in color Doppler mapping. All the patients underwent laparoscopy under 3D-video imaging using Cooper surgical (USA) and Laser optic system (Laser Components USA Inc., USA-Germany) equipment to estimate the pelvic varicose veins, severity degree using retrograde hemodynamic testing (patent for an invention) [18]. The technique allowed one to register venectasia in the pelvic venous plexuses and perform biopsy of varicose vein sections for histological verification of the diagnosis.

2.4. Biochemical measurements

Vein blood sampling in patients with PVI and the control group was performed during laparoscopy equipment (Karl Storz, Germany and Cooper Surgical, USA) and a 3D Laser Optic System equipment (Laser Components USA Inc., USA, Germany). Plasma and erythrocyte hemolysate were used as test material. Blood sampling was performed from the ulnar vein in accordance with the generally accepted requirements.

The concentrations of Th1-inflammatory cytokines TNF-a, IL-1β, IL-2, IL-6, IL-8 and Th2-inflammatory interleukins IL-4, IL-10 were assessed by enzyme immunoassay using monoclonal antibody panels (JSC "Vector-Best," Russia). In addition, we calculated the proinflammatory index (PI),

reflecting the balance of pro- and anti-inflammatory cytokines, as the ratio IL-6/IL-10.

Venous blood was sampled from the cubital vein between 8:00 and 9:00 a.m. after a 12-h overnight fasting period and collected into two tubes containing EDTA (ethylenediaminetetraacetic acid) anticoagulant. Immediately after collection, the blood was centrifuged at 1500 g for 10 min at 4 °C to separate the plasma from erythrocytes. The plasma was removed, and the erythrocytes were washed three times in cold saline solution (0.9% w/v). The erythrocytes were subsequently hemolyzed by adding 9 volumes (v/v) of cold phosphate buffer (50 mM, pH 7.4). Samples were kept frozen at –40 °C for no more than one month for LPO products and antioxidant enzyme parameter determination.

The LPO processes' intensity was determined: Lipid hydroperoxides (LH) and conjugated dienes (CDs) were determined by the spectrophotometric method, and the level of TBA-reactive products (TBARs) of LPO were determined by fluorometric method [19,20]. Levels of LPO products in blood plasma were evaluated. The concentrations of CDs were detected using the absorbance of plasma heptane extracts at 232 nm. The molar absorption coefficient ($K = 2.2 \times 10^5\ M^{-1}\ C^{-1}$) was used for conversion of absorption. The levels of TBARs were determined by reaction with thiobarbituric acid followed by fluorescence intensity measurements at 515 nm (excitation) and 554 nm (emission).

The AOD system state—activity of superoxide dismutase (SOD) [21] and reduced glutathione (GSH) content [22], as well as catalase, glutathione reductase (GR) (GLUTATHIONE REDUCTASE, Randox Laboratories Ltd., UK), glutathione peroxidase (GPO) (GLUTATHIONE PEROXIDASE, Randox Laboratories Ltd., UK), and glutathione-S-transferase (G-S-T) (GLUTATHIONE-S-TRANSFERASE-π, Immunodiagnostik, Germany) activities was determined using by commercial kits. Blood plasma was used to determine catalase, GPO and GR levels, whilst erythrocytes were used to determine GSH, G-S-T and SOD levels. The measurements were made by the spectrofluorophotometer "Shimadzu RF-1501" (Shimadzu Corporation, Japan) and spectrophotometer "Shimadzu RF-1650" (Shimadzu Corporation, Japan). Enzyme immunoassay was performed on a MultiSkan ELX808 microplate reader (Biotek, USA). This work was carried out using the equipment of the Centre of Collective Usage "Center for the Development of Progressive Personalized Health Technologies," Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

2.5. Statistical procedure

Statistical processing was performed using Statistica 10.0 software (Statsoft Inc., USA). Descriptive statistics of the findings were presented as medians (Me) and 25 and 75 quartiles (25%, 75%). Comparison of intergroup differences was performed using the nonparametric Mann-Whitney test with Bonferroni correction. The level of statistical significance was taken as $p < 0.05$.

3. Results

The basic characteristics of the patients with PVI and the control group are shown in Table 1. There were no statistically significant differences in the main groups' characteristics ($p > 0.05$).

Table 1. Characteristics of the patients with PVI and the control group (%).

Characteristics	Control group	Patients with PVI	p
Age mean (SEM)	38.6 (3.7)	32.5 (0.8)	p > 0.05
Irregular menstruation	26%	23%	p > 0.05
Pelvic pain	16%	53%	p > 0.05
Dyspareunia	10%	25%	p > 0.05
Dysuria	10%	7%	p > 0.05
Psycho-emotional disorders	13%	15%	p > 0.05
Disorders of pelvic organs' function	16%	25%	p > 0.05

Note: $p < 0.05$, statistically significant differences with the control group; PVI, pelvic venous insufficiency; SEM, standard error of the mean.

The cytokine profiles in patients with PVI and women in the control group were characterized by the following statistically significant differences: increases in the concentrations of proinflammatory cytokines, IL-6 and IL-8, against a background of rising anti-inflammatory cytokine values (IL-4 and IL-10) (Table 2). There were also significant differences in the IL-6/IL-10 ratio in the form of higher values in patients with PVI.

Table 2. The levels of cytokines in the blood of patients with PVI (Me, 25–75%).

Parameters	Control	Patients with PVI	p
IL-1β, pg/mL	124.70 (113.88; 131.15)	135.10 (125.14; 158.26)	p > 0.05
IL-2, pg/mL	39.63 (33.25; 45.74)	42.57 (38.83; 54.71)	p > 0.05
IL-4, pg/mL	793.76 (762.58; 825.38)	1205.69 (1050.39; 1390.21)	p = 0.038
IL-6, pg/mL	2241 (3147; 3380)	5162 (4968; 5230)	p < 0.0001
IL-8, pg/mL	1151 (1075; 1217)	2149 (1905; 2389)	p = 0.042
IL-10, pg/mL	1145.72 (1067.43; 1271.58)	1603.81 (1420.83; 1849.45) *	p = 0.046
IL-6/IL-10, units	2.85	3.20 *	p = 0.041

Note: $p < 0.05$, statistically significant differences with the control group, IL, interleukin; PVI, pelvic venous insufficiency.

The results of the LPO-AOD processes intensity study showed statistically significant differences in the lipid peroxidation products content in patients with PVI (Table 3). Thus, the primary lipid peroxidation products (CDs) level statistically significantly increased relative to control values. Changes in the content of final TBARs revealed an other difference: a decrease of average TBARs values relative to controls. The content of antioxidant defense parameters in women with PVI also differed statistically significantly (Table 3). The activity of the AOD system main enzyme, SOD, decreased. Catalase activity showed increased values. The glutathione reductase and glutathione peroxidase levels were not statistically significantly different in the studied groups. The reduced form of glutathione (GSH) concentration in patients with PVI differed in showing lower values compared to controls.

Table 3. The level of LPO-AOD components in the blood of patients with PVI (Me, 25–75%).

Parameter	Control	Patients with PVI	p
LH, units	5.19 (5.07–5.3)	5.59 (5.38–5.75)	
CDs, μmol/L	1.85 (1.82–1.86)	5.14 (5.09–5.21)	p = 0.041
TBARs, μmol/L	2.63 (2.56–2.76)	1.11 (1.06–1.17)	p = 0.038
Catalase, μmol/L	41.86 (39.75–44.17)	49.26 (47.63–52.85)	p = 0.041
SOD, units	62.51 (55.20–68.39)	51.89 (50.83–53.97)	p = 0.032
GPO, μmol /g Hb	34.17 (33.95–35.56)	48.95 (48.13–49.38)	p > 0.05
GR, μmol/mL	4.12 (3.94–4.21)	3.04 (3.99–3.05)	p > 0.05
G-S-T, mmol/g Hb	5.21 (4.97–5.38)	5.55 (5.20–6.88)	
GSH, mmol/mL	3.54 (3.35–4.72)	2.91 (2.84–3.06)	p = 0.044

Note: *, $p < 0.05$, statistically significant differences with the control group; CDs, conjugated dienes; GR, glutathione reductase; GPO, glutathione peroxidase; G-S-T, glutathione-S-transferase; GSH, reduced glutathione; LH, lipid hydroperoxides; PVI, pelvic venous insufficiency; SOD, superoxide dismutase; TBARs, thiobarbituric acid reactants.

4. Discussion

PVI has a chronic course and is difficult to treat, which is due to the variety of factors affecting the venous wall [2,3,23]. In the blood of patients with PVI initial manifestations, we noted cytokine profile changes: increased concentrations of both proinflammatory and anti-inflammatory interleukins. In the blood of patients with PVI, the IL-6/IL-10 ratio was characterized by the prevalence of pro-inflammatory over anti-inflammatory factors. Venous vessels, unlike arterial ones, are characterized by lower blood flow and tone indices [1]. Under physiological conditions, functioning veins, blood consumes 2 times more oxygen than arteries, while under conditions of venous insufficiency, this requirement increases by 3 times [4]. All this leads to functional restructuring of vascular endothelium, which develops by several stages. The initial stages, as a rule, are characterized by increased endothelial cells synthetic activity, while there are no barrier permeability disturbances [24]. Venous stasis and microcirculation disorders cause local ischemia, and hypoxia triggers the mechanism of leukocyte activation with inflammatory cytokines production, which results in increased inflammation in the affected area [7,14,25,26]. Cytokines are also able to induce acute-phase reactions both at the local and at the systemic level [27]. Cytokines are also involved in leukocyte activation, which leads to the release of free radicals, activation of proteases and subsequent smooth muscle cell degradation [6,7]. Cytokines activate specific receptors and modulate the functions of various cells and tissues. Proinflammatory factors can exert their influence on cells by regulating the transcription factor activation of proinflammatory genes [10]. This leads to further endothelial damage, in the form of connective tissue disorganization and thickening of the venous wall media [11]. In our study, a parallel increase of anti-inflammatory cytokines was found in patients with initial manifestations of PVI, which can be regarded as a compensatory reaction. However, the proinflammatory to anti-inflammatory factors ratio index was increased in patients with PVI.

It was found out that venous insufficiency is accompanied by intensification of lipid peroxidation processes [10,11]. Changes in the lipid peroxidation system may be an important factor in the development and progression of this pathological condition [13]. Studies of PVI pathogenesis proved that decreased oxygen saturation and reactive oxygen species production can also be inductive factors of pelvic veins, pathological changes in women [16,28]. Developing tissue ischemia and endothelial

dysfunction can also contribute to further intensification of free radical reactions that lead to a decrease of regenerative capabilities [29]. We have found an increase of CDs (primary LPO products) values combined with reduced final products values, catalase activity compensatory increase and reduced activity of SOD and GSH. The biological effect of free radicals is realized both through their direct effect on cellular biostructures and through LPO products (lipid hydroperoxides, conjugated dienes, aldehydes) formed at different stages of the chain reaction [30]. Likely negative effects may be deformation of biomembranes, changes in the dynamics of ion transport, changes in enzyme activity and other pathological phenomena [29,30,31,32]. Higher values of catalase activity in PVI may indicate the presence of compensatory reactions in response to the LPO products increase. There are studies indicating increased catalase and malonic dialdehyde levels in patients with varicose veins, while the activities of SOD, GPO and G-S-T enzymes showed no statistically significant differences, which was explained by a compensatory response [32,33]. GSH is the main antioxidant of erythrocytes, serves as a coenzyme in methemoglobin reduction into functionally active hemoglobin and detoxifies peroxides and hydroperoxides that are formed during the reactive oxygen species reaction with membranes, unsaturated fatty acids [34,35]. The apparent deficiency of this antioxidant may indicate the presence of negative changes in the activity of the AOD system, which should be taken into account.

5. Conclusions

The results of the women pelvic venous insufficiency study indicate simultaneous changes in the cytokine profile and multidirectional changes in the indicators of the LPO system state in the initial stages of the disease. These changes involved increased fractions of proinflammatory, anti-inflammatory cytokines and caused an increased IL-6/IL-10 ratio. Primary lipid peroxidation products showed increase values accompanied by a compensatory increase in catalase activity, along with decreased SOD activity and reduced glutathione. Probably, the control of these changes in patients with PVI should be an important component of preventive measures in the early stages of the disease.

Acknowledgments

None.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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Series introduction: HIV/AIDS and mental health

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Keywords: biosocial; burden of illness; HIV/AIDS; mental health; PLWHA; syndemic(s); substance use

As we enter the fifth decade of the human immunodeficiency virus (HIV) pandemic, HIV continues to cause substantial morbidity, particularly in populations with disproportionate and sustained exposure to structural inequities. This is repeatedly observed when the interplay between HIV infection and psychiatric illness is examined, particularly in the context of noxious social conditions. However, when the HIV epidemic evolved in the 1980s, it was largely recognized as an isolated disease and psychiatric features were largely relegated to the psychological impacts of the adjustment reaction to a positive diagnosis and the stigma of living with HIV. It has since become evident that HIV infection has notable neuropsychiatric sequelae throughout the course of illness, is transmitted through complex biosocial interactions which play an instrumental role in shaping the course of illness, and effective management requires integrated and intersectional approaches to care [1–6]. Although the high case fatality rate that initially characterized the illness has since plummeted, there are still 1.5 million new cases a year globally (UNAIDS), with a disproportionate number of the cases occurring amongst marginalized and stigmatized populations [7].

This is further exacerbated by COVID-19 pandemic related health service reductions and delays, redirected public health foci, increased social isolation and deepening fractures in public infrastructure in the context of the ongoing COVID-19 Pandemic. The unique impact of the COVID-19 Pandemic on people living with HIV/AIDS (PLWHA) is further explored in this Series. The advent of highly active antiretroviral therapy (HAART) has resulted in the transformation from acute infectious illness to a post-acute era in which HIV infection is a chronic disease that faces a new challenge: ageing with HIV. This Series explores ageing with HIV and elucidates the unique needs of PLWHA as they age with a chronic disease. Ageing with HIV is associated with increased risks of neurocognitive impairment which is heightened by treatment non-adherence [8,9], yet psychiatric care is still a lagging component of HIV care. Care should ideally be delivered through an integrated multispecialty care model in order to optimize patient outcomes, particularly as multisystem morbidity is the norm rather than the exception with chronic HIV infection.

Despite the longevity conferred by treatment, PLWHA continue to experience significantly increased rates of psychiatric illness, which is not well accounted for by the traditional biomedical model. Rather, the elevated rates of psychiatric illness amongst other adverse health conditions observed in the most vulnerable populations of PLWHA reflect a dynamic state of synergistic epidemics, or syndemics [1–6]. The process of syndemogenesis is characterized by distinct synergistic biosocial processes in which adverse environmental contexts interact with the biopsychosocial disease process to yield a multiplicative effect of excess disease burden clustered in vulnerable populations [1,2,5,10].

The complex biosocial environment, pervasive stigma of HIV, and the transmutation of these factors at the biologic level drive an excess burden of addictions and other psychiatric comorbidity in PLWHA. Conversely, people with persistent psychiatric illness are at increased risk of HIV infection. People with HIV and/or AIDS are uniquely vulnerable to psychiatric conditions both as a result of the pathophysiology of the infection itself, the experience of illness and the neuropsychiatric sequelae of antiretroviral medication [5,11–14]. The experience of illness encompasses significant adjustment reactions associated with a new HIV diagnosis, anxiety and depressive disorders associated with living with HIV/AIDS, neuropsychiatric sequelae of HAART, substance use disorders as a maladaptive means of coping with the diagnosis as well as the role of substance use as a syndemic generator in the acquisition and clustering of HIV with other conditions.

The complex psychiatric synergies associated with HIV/AIDS constitute a core component of the burden of living with HIV/AIDS, with considerable impact on transmission, disease progression and severity, treatment costs, adherence to treatment, and prognosis [2,5,8,9,11–14]. As such, the interaction of HIV/AIDS and psychiatric disorders constitutes an essential area in which further momentum is required. This special issue will focus on the complexities of HIV infection and mental health, explored through the following topics in the Series:

1. HIV Psychiatry—the missing link to HIV prevention and comprehensive care
2. Syndemogenesis: a dash of exclusion, a pinch of inequity and a heaping spoon of synergistic interactions: exclusion, inequity and syndemogenesis
3. HIV, multisystem morbidity and mental health
4. Ageing with HIV: neurocognitive impacts
5. Neuropsychiatric sequelae of medication non-adherence
6. Compounding Impacts: the interplay between the COVID-19 pandemic and people living with HIV/AIDS
7. Substance use disorders and HIV/AIDS

Conflict of interest

The author declares no conflicts of interest in this paper.

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Associated outcomes of various iterations of the dedicated orthopaedic trauma room: a literature review

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ABSTRACT

Scheduling urgent, orthopaedic trauma cases has long been a challenge for health care institutions. Traditionally, these cases are scheduled for an operating room (OR) slot in the middle of the night, by "bumping" elective cases to later in the day, by adding a case on after-hours, or by delaying the case for several days until an OR becomes available. As a solution to the challenges facing traditional scheduling modules, trauma centers around the country have instituted the use of a dedicated orthopaedic trauma room (DOTR). While there are multiple studies analyzing the effects of DOTRs on various outcomes, there is not a centralized review of these studies. This paper will serve as a review of the various models of the DOTR as well as the effect of the DOTR on after-hours procedures, time to surgery (TTS), duration of surgery (DOS), length of stay (LOS), cost, and surgical complications. An extensive review of the literature was performed through PubMed and Embase. 17 studies were found to meet eligibility criteria. This review suggests that DOTRs have favorable effects on after-hours procedures, cost, and surgical complications. There is variability in the data regarding the effect on TTS, DOS, and LOS.

Keywords: dedicated orthopaedic trauma room; dedicated orthopaedic trauma list; urgent surgery; patient safety; after-hours procedures; duration of surgery; time to surgery; length of stay; complications; cost

Abbreviations:
ASA: American Society of Anesthesiologists; ACS NSQIP: American College of Surgeons National Surgery Quality Improvement Program; OR: Operating room; NPO: Nil per os; DOTR: Dedicated orthopaedic trauma room; DOTL: Dedicated orthopaedic trauma list; TTS: Time to surgery; DOS: Duration of surgery; LOS: Length of stay; FRR: Fracture reduction room; FSDF: Femoral shaft and distal femur fractures; ORIF: Open reduction and internal fixation

1. Introduction

The designation of "urgent" to a surgical case implies that the case is neither emergent, nor elective. Emergency status is designated as part of the ASA Physical Status classification system, whereas elective status is defined as a scheduled surgery in which the patient is specifically brought to a medical facility for the procedure. For general surgery, the ACS NSQIP protocols state that operations be labeled "urgent" when they do not meet the emergency or elective criteria [1]. The ACS Trauma Center Guidelines require for there to be an available OR for emergencies, but there are no written guidelines regarding urgent surgery [2].

Scheduling urgent trauma cases has long been a challenge for health care institutions. Traditionally, these cases are scheduled for an OR slot in the middle of the night, by "bumping" elective cases to later in the day, by adding a case on after-hours, or by delaying the case for several days until an OR becomes available. With this traditional scheduling model, urgent cases across all surgical specialties are competing for OR availability. Orthopaedic trauma is often deemed "less urgent" than trauma that falls into other specialty categories such as general or neurosurgical cases, resulting in a large disruption in orthopaedic trauma surgical care. In countries with universal health care systems, patients may wait days for urgent surgery [3,4]. The traditional scheduling model has deleterious ramifications affecting the patient, surgeon, and institution, for both the urgent and elective cases. Surgical delays can cause increased wait time for the patient, lengthening the time spent NPO and delaying time to rehabilitation [5]. In addition, patient outcomes may be affected by undergoing an after-hours procedure [6]. The unpredictable nature of the traditional scheduling model also affects surgeons by increasing the need to operate after-hours, including cases in the middle of the night after a full day of work and during "off duty" hours. Otherwise, elective cases can be bumped at the expense of significant disruption to the flow of all Ors, the surgeon's individual daily schedule, and the patient's time. As a result of this disruption, it can be difficult to recruit and maintain fellowship trained orthopaedic traumatologists and senior, experienced surgeons due to lifestyle detriments and burnout [7]. The traditional scheduling model also has effects at the institutional level. Increased cost can occur secondary to higher overtime and nighttime staffing. In addition, patients must occupy a bed either in the emergency department or on the floor while awaiting surgery, leading to usage of finite hospital resources, further contributing to the overall cost of care.

As a solution to these challenges facing traditional scheduling models, trauma centers around the country have instituted the use of a dedicated orthopaedic trauma room (DOTR). The DOTR model was first described in the United States by Bhattacharyya et al [7]. It was originally defined as an OR scheduling model that ensures a daytime OR is available for urgent orthopaedic trauma. This is typically achieved by blocking off a certain amount of time on weekdays, with no elective cases scheduled, to be under the full control by the day's attending traumatologist. Featherall et al. surveyed the top 20 US hospitals and found that 70% use an iteration of the DOTR [5]. Various models of the DOTR have been implemented around the world. In countries such as Australia and the United Kingdom, hospital systems have implemented the use of a dedicated orthopaedic trauma list (DOTL). The DOTL operates in the same fashion as a DOTR, where an OR remains un-booked and available for trauma cases to be scheduled by the attending specialist [8]. Bhattacharyya et al. described how the DOTR was initially implemented with three goals in mind: to (1) improve quality of care, (2) improve efficiency, and (3) recruit and retain fellowship trained orthopaedic surgeons [7].

While there are multiple studies analyzing the effects of DOTRs/DOTLs on various outcomes, there is not a centralized review of said studies. This paper will serve as a review of the various models of the DOTR/DOTL as well as the effect of the DOTR/DOTL on after-hours procedures, time to surgery, duration of surgery, length of stay, cost, and surgical complications.

2. Materials and methods

2.1. Search strategy

An extensive review of the literature was performed through PubMed and Embase. Key words used in

the search included (emergency operating room AND orthopedic trauma) OR (emergency operating room AND orthopaedic trauma) OR (urgent operating room AND orthopedic trauma) OR (urgent operating room AND orthopaedic trauma) OR (dedicated orthopaedic trauma room) OR (dedicated orthopedic trauma list) OR (dedicated orthopaedic trauma list) OR (dedicated orthopaedic operating room) OR (dedicated orthopaedic operating room). Results were limited to studies published between 2005 and 2022, in English.

2.2. Eligibility criteria

Studies were included in the review if they were published in English, involved clinical research, and reported the use of a dedicated operating room at a regular interval throughout the week, specifically for orthopaedic trauma.

2.3. Statistical significance

For the purpose of this review, reported outcomes were considered statistically significant if $P \leq 0.05$.

3. Results

3.1. Study selection (see Figure 1)

After the removal of duplicates, there were 700 articles left for review. Titles and abstracts were screened for all 700 articles, leaving 28 articles left for review. Full text review was performed on all 28 articles; 17 articles met the full eligibility criteria. The PRISMA flow diagram is shown in Figure 1.

3.2. Study characteristics (see Table 1)

All 17 studies that met the inclusion criteria were retrospective in design. 14 out of 17 (82%) studies were performed at level 1 trauma centers, while the remaining 3 were at a satellite hospital of a tertiary care center, a level 2 trauma center, or a regional hospital (6%, respectively). Additional descriptive information of all 17 studies can be found in Table 1.

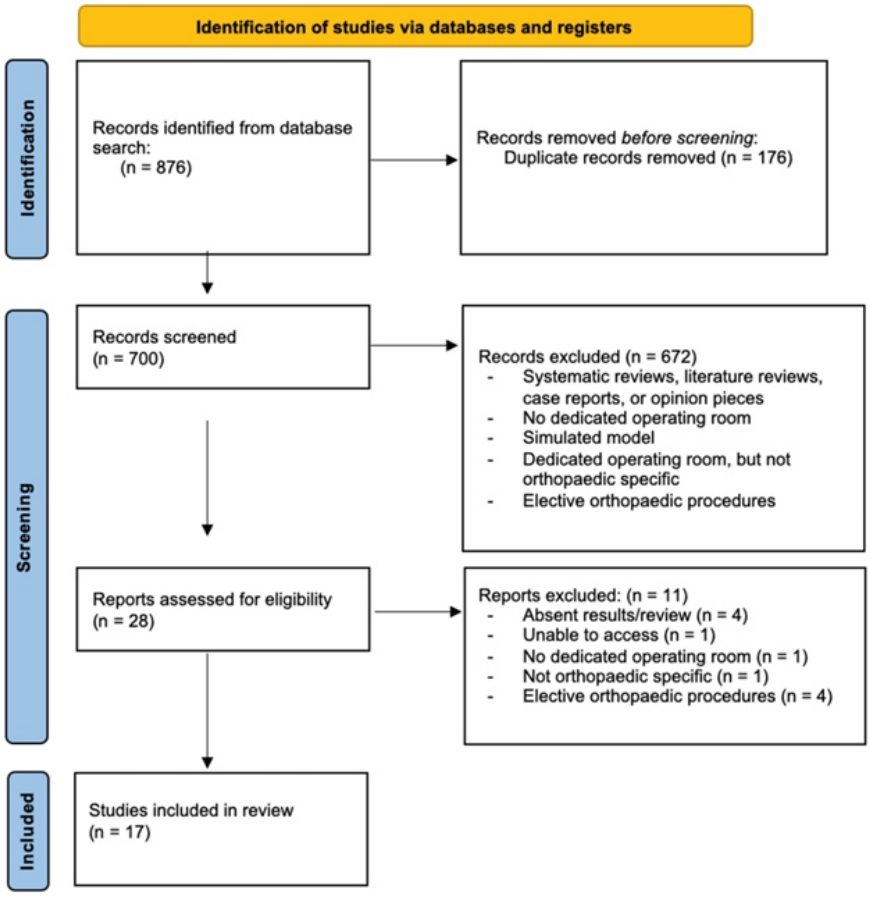

Figure 1. PRISMA flow diagram for systematic review.

Table 1. Study characteristics.

Author	Year	Country	Study design	Sample size	Institution classification	Model of DOTR
Elder et al.	2005	Canada	Retrospective	701	Level I trauma center	Mon–Fri DOTR; first 4 hour block of operative day
Bhattacharyya et al.	2006	United States	Retrospective	217	Level I trauma center	6 days per week; 7:45 am–5:00 pm
Lemos et al.	2007	Canada	Retrospective	457	University trauma center	DOTR 4 days per week
Wixted et al.	2008	United States	Retrospective	3845	Level I trauma center	Mon–Fri DOTR
Chacko et al.	2011	United States	Retrospective	767	Level I trauma center	Daytime DOTR
Roberts et al.	2015	United States	Retrospective	111	Level I academic trauma center	Mon–Fri DOTR; 7:30 am–4:00 pm
Runner et al.	2016	United States	Retrospective	455	Urban level I trauma center	Saturday DOTR
Taylor et al.	2016	Canada	Retrospective	609	Tertiary care center	Weekend DOTR
Brusalis et al.	2017	United States	Retrospective	1469	Level-I pediatric trauma center	Mon–Fri; 7:30 am–5:00 pm
Steeby et al.	2018	United States	Retrospective	347	University Level I trauma center	Daily DOTR

Waters et al.	2018	United States	Retrospective	480	Satellite campus of pediatric tertiary care center	DOTR 3 days per week in the summer and 2 days per week remainder of the year; 7:30 am–5:00 pm
Whitlock et al.	2019	United States	Retrospective	40	Tertiary care center	Fracture reduction room; Tuesday at 7:30 am
Knight et al.	2021	Australia	Retrospective	422	Major referral center	DOTL 8:30 am–5:00 pm 6 days per week
McDonald et al.	2021	United States	Retrospective	431	Level II community trauma center	6:00 am–9:00 am DOTR Mon–Fri
Thompson et al.	2021	Australia	Retrospective	242	Small, regional hospital	Twice weekly DOTL
Cloud et al.	2022	United States	Retrospective	128	University-based level 1 trauma center	Weekday DOTR
Denisiuk et al.	2022	United States	Retrospective	2928	Level 1 trauma center	Daily DOTR from 7:30 am–5:00 pm

4. Discussion

4.1. Various models of DOTR (see Table 1)

The first DOTR described in the literature was instituted prior to 1991 in a Canadian tertiary care trauma center [3]. This model consisted of a DOTR Monday through Friday during the first 4-hour block of the operative day. In 1999, Massachusetts General Hospital instituted a DOTR, operating from 7:45 am to 5pm six days per week [7]. At both institutions, the DOTR was controlled by staff orthopaedic traumatologists on a rotating basis. Nighttime call was provided by the following day's surgeon. Since these initial models were described, multiple centers have implemented identical or similar DOTRs [9–15]. As DOTRs gained popularity, various models have been implemented to meet the needs of a specific institution. Featherall et al. described a center with a daily DOTR that remained open unless no orthopaedic trauma cases were booked by 5:00pm the night prior. At that point, elective cases were permitted for scheduling [5]. Thompson et al. reported an institution with a twice weekly DOTL, ensuring an available OR for trauma cases as they presented [4]. Runner et. al implemented a Saturday DOTR in a center that previously only had 3 active trauma ORs on the weekend, one that was reserved for general trauma and the other 2 shared by all specialties [16]. Similarly, Taylor et al. created a weekend DOTR at a level II community trauma center [17]. McDonald et al. introduced an abbreviated version of the DOTR from 6 am to 9 am, Monday through Friday, allowing for one case to be scheduled before the start of the elective schedule [18]. Rather than a general DOTR, Whitlock et al. described a dedicated fracture reduction room (FRR) in a fluoroscopy suite at a pediatric center. The FRR was operated on Tuesdays each week [19].

While all the above DOTRs are located at the primary hospital location, Waters et al. described a unique iteration of the DOTR by creating a dedicated satellite trauma room for a pediatric tertiary care center [20]. The DOTR (7:30 am to 5 pm) was at a satellite hospital for 3 days per week in the summer and 2 days per week the rest of the year. Non-emergency, non-multitrauma operative fracture cases were considered for satellite referral with an extensive list of exclusion and inclusion criteria.

In addition, short elective cases were permitted when there were openings in the schedule. This study showed no technical or clinical intraoperative complications as a result of care at the satellite location, no cases of compartment syndrome, and no cases requiring transfer back to the tertiary center. The introduction of the satellite trauma room allowed for decreased volume at the tertiary center by referrals that did not require level 1 trauma care.

See Table 1 describing all the models of the DOTR/DOTL that met eligibility requirements.

4.2. After-hours procedures (see Table 2)

One of the main challenges of the traditional scheduling model is the lack of daytime OR availability for urgent trauma, necessitating the need for after-hours procedures. After-hours procedures have been shown to be associated with worse outcomes, increased complication rates, and increased duration of surgery [6]. Ricci et al. has studied the effect of after-hours surgery on outcomes for femoral and tibial shaft fractures via a prospective comparative study of 243 cases. Results showed that unplanned reoperations were two times higher in the afterhours group compared to the daytime group. In addition, painful hardware was removed in 27% of the after-hours group versus 3% in the daytime group [6]. Another study found that the mean duration of surgery was 14 minutes longer when performed after-hours (P = 0.003) and there were statistically significant higher rates of complications including pneumonia, pulmonary embolism, and surgical site infection after-hours [18].

Table 2. After-hours procedures.

Author	Injury	Percentage change of after-hours procedures after DOTR/DOTL	P value
Waters et al.	–	–	–
Brusalis et al.	Supracondylar humeral fractures Lateral condylar fractures Tibial fractures	Minus 48%	<0.001
Steeby et al.	Open tibia OR open femur fracture	–	–
Runner et al.	Femur *or* tibial fractures	Monday caseload: minus 6.7%	NS; 0.062
Lemos et al.	–	–	–
McDonald et al.	Femoral neck, intertrochanteric, *or* subtrochanteric femur fractures	Minus 12.8%	0.036
Bhattacharyya et al.	Intertrochanteric hip fractures	Minus 21%	<0.01
Taylor et al.	–	–	–
Whitlock et al.	–	–	–
Wixted et al.	Isolated, closed, femoral shaft fractures	7 pm to 12 am: minus 16% 12 am to 7 am: minus 44%	0.0022 0.003
Chacko et al.	Intertrochanteric, subtrochanteric, *or* femoral neck fractures	Numbers reported but not analyzed	–
Elder et al.	–	–	–
Thompson et al.	All procedures utilizing trauma list	Minus 14.7%	<0.05
Knight et al.	Closed tibial fractures	Decreasing trend	NS
Roberts et al.	Femoral neck fracture	Minus 47.4%	<0.001
Cloud et al.	–	–	–
Denisiuk et al.	–	–	–

Note: NS indicates “not significant”; Dashes indicate the measure was not studied.

As a result of the data indicating worsened outcomes associated with after-hours procedures, a primary goal for the implementation of a DOTR is to reduce after-hours procedures and therefore mitigate the associated adverse effects. Of the 17 studies included in this review, 9 reported an outcome related to percent change of after-hours procedures. 6 out of 9 (67%) reported a statistically significant decrease in after-hours procedures, 2 out of 9 (22%) reported a decreasing trend of after-hours procedures, and 1 out of 9 (11%) reported number of after-hours procedures but did not analyze the data. No studies reported an increase of after-hours procedures. Bhattacharyya et al. found that hip fracture cases performed after-hours was reduced from 29% to 8% ($P < 0.01$) [7]. Brusalis et. al reported a 48% reduction ($P < 0.001$) of after hour procedures following the development of a Monday through Friday DOTR (7:30 am to 5 pm) in a pediatric center [9]. Similarly, Wixted et al. found a 16% decrease in cases performed from 7 pm to 12 am ($P = 0.0022$) and a 44% decrease in cases performed between 12 am and 7 am ($P = 0.003$) after the development of a Monday through Friday DOTR [12]. Roberts et al. also described a decrease in after hours operations from 66.7% to 19.3% ($P < 0.001$) after the creation of a Monday through Friday DOTR [14]. At an institution that only implemented a DOTR for one case per morning, there was a decrease in after-hours surgery from 32.4% to 19.6% ($P = 0.036$) [18].

The development of a Saturday DOTR allowed for 59% more cases to be performed on Saturdays, creating a trend towards decreased Monday caseloads and therefore a decrease in cases that must be performed after-hours [16]. A twice weekly trauma list resulted in nearly half the number of operations performed on the weekends compared to before the implementation of the trauma list ($P < 0.001$). In addition, operations performed after 16:00 hours reduced from 50.5% to 35.8% ($P < 0.05$) [4]. In summary, the majority of studies that described percent change of after-hours procedures as an outcome measure reported a statistically significant decrease.

4.3. Time to surgery (see Table 3)

Time to surgery (TTS) is often used as a quality measure for operating room efficiency. With the traditional scheduling model, a lack of OR availability has historically led to increased TTS. It was hypothesized that a DOTR would provide an available OR for urgent trauma and therefore decrease the TTS. However, some have concerns that the guaranteed availability of a daytime OR would result in a delay of the case to the following day, regardless of the urgency [21].

Table 3. Time to surgery.

Author	Injury	Change in time to surgery after DOTR/DOTL*	P value
Waters et al.	–	–	–
Brusalis et al.	Supracondylar humeral fractures	Minus 0.7 hours	0.039
	Lateral condylar fractures	Minus 1.7 hours	0.037
	Tibial fractures	Minus 11.3 hours	0.041
Steeby et al.	Open tibia fracture *or* open femur fracture	+ 7.5 hours	0.004
Runner et al.	Femur fracture *or* tibial fracture	Minus 25.1 hours	NS; 0.06
Lemos et al.	Subcapital hip fractures	+ 15.6 hours	0.006
McDonald et al.	Femoral neck, intertrochanteric, *or* subtrochanteric femur fractures	No significant difference	–

Bhattacharyya et al.	–	–	–
Taylor et al.	Subcapital fracture *or* femoral neck fracture *or* basicervical fracture *or* intertrochanteric fracture *or* subtrochanteric extension fracture	Minus 3 hours	NS
Whitlock et al.	Displaced, closed pediatric forearm fractures	No significant difference	–
Wixted et al.	Isolated, closed, femoral shaft fractures	+ 0.7 hours	NS

Continued on next page

Author	**Injury**	**Change in time to surgery after DOTR/DOTL***	**P value**
Chacko et al.	–	–	–
Elder et al.	Displaced subcapital hip fractures	Minus 27.2 hours	<0.0001
Thompson et al.	All procedures utilizing trauma list	No significant difference	–
Knight et al.	Closed tibial fractures	+ 18 hours	0.01
Roberts et al.	–	–	–
Cloud et al.	Diaphyseal femur fracture	Minus 424 minutes**	0.002
Denisiuk et al.	Femoral neck fracture	Minus 6.2 hours	0.039
	Pertrochanteric hip fracture	Minus 1.6 hours	<0.001
	FSDF fracture	Minus 3.6 hours	0.046

Note: *Value indicates mean change unless otherwise indicated; **Value reported in median change; NS indicates "not significant"; Dashes indicate the measure was not studied.

Of the 17 studies included in this review, 13 reported an outcome related to time to surgery. 4 out of 13 (31%) reported a statistically significant decrease in time to surgery, 3 out of 13 (23%) reported a statistically significant increase in time to surgery, and 6 out of 13 (46%) reported no statistically significant difference. At a pediatric center with a Monday through Friday DOTR, there was a statistically significant reduction in mean TTS for supracondylar humeral fractures, lateral condylar fractures, and tibial fractures [9]. Serving as a control, the same study demonstrated no statistically significant difference in TTS for urgent appendectomies during that time. At a different center, patients admitted on a Friday were found to have a 25.1-hour mean reduction ($P = 0.06$) in TTS following the development of a Saturday DOTR [16]. Similarly, Elder et al. found a decrease in TTS, with a mean of 56.5 hours at a center without a DOTR versus 29.3 hours at a center utilizing a DOTR ($P < 0.001$) [3]. Taylor et al. found a decreasing trend in mean TTS following the implementation of a weekend DOTR [17]. Cloud et al. demonstrated a statistically significant decrease in median time to intramedullary nailing of diaphyseal femur fractures, which allowed for a statistically significant decrease in placement of temporary external fixators from 15% to 2.9% [22]. Similarly, Denisiuk et al. demonstrated a statistically significant mean decrease in TTS for pertrochanteric hip, femoral neck, and femoral shaft and distal femur fractures (FSDF) after the implantation of a DOTR [23].

Alternatively, Steeby et al. found that following the implementation of a DOTR, the average time to debridement for open tibia and femur fractures was significantly longer in the DOTR group versus the non-DOTR group (12.9 hours vs 5.4 hours, P = 0.044) [11]. Additionally, patients were 9 times less likely to undergo debridement within 6 hours when in the DOTR group. However, rates of debridement in 24 hours were similar between the on-call OR and the DOTR and the incidence of malunion, infection, or amputation between the DOTR group and the on-call OR was equivocal. Similarly, Lemos et al. found an increase in TTS after implementing a DOTR 4 days per week, with the mean TTS 72.1 hours after implementation versus 56.5 hours before (P = 0.006) [10]. In patients with tibial fractures, Knight et al. observed an increased TTS from 11.04 hours to 29.04 hours following the creation of an orthopaedic trauma list (P = 0.01) [15]. Knight et al. also analyzed the effect of the trauma list on the time from referral to surgery for patients with hand tendon injuries, showing an increase of 1.06 days to 2.82 days after implementation (P = 0.001). As mentioned above, multiple studies reported no significant difference in TTS after the implementation of a DOTR/DOTL [4,12,18,19].

In summary, there is variability in the data regarding the effect of a DOTR/DOTL on time to surgery.

4.4. Duration of surgery (see Table 4)

With the development of DOTRs, it was hypothesized that duration of surgery (DOS) would be decreased due to availability of familiar operating room staff, presence of equipment representatives, and less surgeon fatigue.

Table 4. Duration of surgery.

Author	Surgical procedure	Change in mean duration of surgery after DOTR/DOTL	P value
Waters et al.	–	–	–
Brusalis et al.	ORIF of radius & ulna *or* closed reduction and percutaneous pinning of supracondylar humerus fracture *or* ORIF of lateral condyle *or* tibia fracture treated with intramedullary elastic nails *or* femur fracture treated with intramedullary elastic nails	No significant difference	–
Steeby et al.	–	–	–
Runner et al.	–	–	–
Lemos et al.	Hip hemiarthroplasty	+ 10 min	0.006
McDonald et al.	Cannulated screw fixation *or* cephalomedullary nailing *or* dynamic hip screw *or* hemiarthroplasty *or* total hip arthroplasty	No significant difference	–
Bhattacharyya et al.	–	–	–
Taylor et al.	Surgical fixation for hip fracture	No significant difference	–
Whitlock et al.	–	–	–

Wixted et al.	Femoral shaft fracture treated with intramedullary nailing	+ 21 min	NS; 0.266
Chacko et al.	Dynamic hip system	Minus 22 min	<0.01
Elder et al.	Hemiarthroplasty	Minus 17 min	<0.0001
Thompson et al.	–	–	–
Knight et al.	Intramedullary tibial nail insertion	No significant difference	–
Roberts et al.	Hemiarthroplasty OR ORIF	No significant difference	–
Cloud et al.	Intramedullary nailing for femur fracture	No significant difference	–
Denisiuk et al.	–	–	–

Note: NS indicates "not significant"; Dashes indicate the measure was not studied.

Of the 17 studies included in this review, 10 reported an outcome related to duration of surgery. 7 out of 10 (70%) reported no statistically significant difference, 2 out of 10 (20%) reported a statistically significant decrease in duration of surgery, and 1 out of 10 (10%) reported a statistically significant increase in duration of surgery. Chacko et al. found a statistically significant decrease in the duration of dynamic hip procedures performed during the day compared to the nighttime group, in addition to a statistically significant decrease after the DOTR became available [13]. Similarly, Elder et al. found the mean DOS for hemiarthroplasties to decrease from 77 minutes to 60 minutes ($P < 0.0001$) after the development of a DOTR [3]. In both cases, decreased DOS was associated with decreased blood loss in procedures. Alternatively, Lemos et al. reported an on average 10-minute increase in the DOS for hemiarthroplasties after introducing a DOTR [10]. Similarly, Wixted et al. found a 21-minute increase in intramedullary nailing following implementation of the DOTR, however these results were not statistically significant ($P = 0.27$) [12]. As noted above, multiple other studies reported no significant difference in the DOS [9,14,15,17,18,22]. In summary, the majority of studies that described DOS as an outcome measure reported no significant effect of a DOTR on DOS.

4.5. Length of stay (see Table 5)

By providing increased OR availability, it was originally hypothesized that the implementation of a DOTR would result in a decreased length of stay (LOS) for trauma patients [7]. Of the 17 studies included in this review, 14 reported an outcome related to LOS. 7 out of 14 (50%) reported a statistically significant decrease in LOS, 1 out of 14 (7%) reported a statistically significant increase in LOS, and 6 out of 14 (43%) reported no statistically significant difference.

Brusalis et al. described a decrease in inpatient hospitalization by 5.6 hours ($P < 0.001$) after implementing a Monday through Friday DOTR at a pediatric center [9]. This seemingly minor decrease in LOS resulted in significant cost savings per patient (discussed further below). At a different center, patients undergoing hip hemiarthroplasty had a decreased LOS by 4.6 days ($P = 0.04$) after the implementation of a Monday through Friday DOTR [14]. At a center where a DOTR was only implemented on Saturdays, Runner et al. found a significant decrease of LOS by 2.7 days ($P = 0.018$) [16]. In addition, Taylor et al. found a significant decrease in mean LOS from 11.6 days to 9.4 days ($P = 0.005$) after the implementation of a weekend DOTR [17]. Thompson et al. reported that at an institution with a twice weekly DOTL, patients on the DOTL stayed on average for 3 less days than those not on the DOTL ($P < 0.05$) [4]. Denisiuk et al. also demonstrated a statistically significant decrease in LOS for

femoral neck fractures and pertrochanteric hip fractures. Of note, after the implementation of a DOTR there was an increased emergency department LOS [23]. Three studies reported a trend towards decreased LOS, however results were not significant [11,15,22]. At a pediatric center that developed a weekly, dedicated fracture reduction room, time from admission to discharge decreased by 67 minutes on average ($P < 0.001$) [19].

Table 5. Length of stay.

Author	Injury	Change in length of stay after DOTR/DOTL*	P value
Waters et al.	–	–	–
Brusalis et al.	Radius/ulnar fracture *or* supracondylar humerus fracture *or* lateral condyle fracture *or* tibia fracture *or* femur fracture	Minus 5.6 hours	<0.001
Steeby et al.	Open tibia fracture *or* open femur fracture	Minus 2.2 days	NS
Runner et al.	Femur fracture *or* tibia fracture	Minus 2.7 days	0.018
Lemos et al.	Subcapital hip fractures	+ 4 days	NS; 0.14
McDonald et al.	Femoral neck *or* intertrochanteric *or* subtrochanteric femur fractures	No significant difference	–
Bhattacharyya et al.	–	–	–
Taylor et al.	Subcapital fracture *or* femoral neck fracture *or* basicervical fracture *or* intertrochanteric fracture *or* subtrochanteric extension fracture	Minus 2.2 days	0.005
Whitlock et al.	Displaced, closed pediatric forearm fractures	Minus 67 min (time from admit to discharge)	<0.001
Wixted et al.	–	–	–
Chacko et al.	Intertrochanteric *or* subtrochanteric *or* femoral neck fractures	No significant difference	–
Elder et al.	Displaced subcapital hip fractures	+ 4 days	0.02
Thompson et al.	All procedures utilizing trauma list	Minus 3 days	<0.05
Knight et al.	Closed tibial fractures	Minus 0.4 days	NS
Roberts et al.	Femoral neck fracture	Minus 4.6 days	0.04
Cloud et al.	Diaphyseal femur fracture	Minus 1.5 days	0.158
Denisiuk et al.	Femoral neck fracture	0.93**	0.044
	Pertrochanteric hip fracture	0.86	<0.001
	FSDF fracture	1.00	0.837

Note: *Value indicates mean change unless otherwise indicated; **Value reported as relative risk (RR); RR < 1.0 indicates lower likelihood in post-DOTR period; NS indicates “not significant”; Dashes indicate the measure was not studied.

Contradictorily, the LOS for patients with low energy femoral neck fractures at one institution was found to significantly increase following the development of a DOTR by an average of 4 days (P = 0.02) [3]. It should be noted however, that patients were more likely to be discharged home rather than to another health care center after the implementation of the DOTR compared to before. Lemos et al. reported a 4 day increase in LOS following the implementation of the DOTR, however results were not statistically significant [10]. As noted above, multiple studies reported no significant difference [13,18].Although the trend was evident for a decrease in the LOS, the majority of the studies did not report a statistically significant change in the setting of a DOTR/DOTL or did not report on this outcome measure.

4.6. Cost

Hesitation to implement a DOTR has been centered around concerns that the opportunity cost is too high to block off time when an OR could be used for lucrative elective cases [5]. Moody et al. published the first study to document the per minute cost of running a DOTR with the intention of defining the value of DOTRs [24]. They found that the total per minute cost was $16.21 at their level II trauma center, without including professional fees of the anesthesiologist or surgeon. Of the 17 studies included in this review, 4 reported an outcome related to cost. All 4 studies described a reduction in cost as a result of a DOTR/DOTL. Brusalis et al. calculated that the decreased LOS associated with the DOTR for pediatric trauma patients resulted in a mean cost reduction of $1,251 per patient [9]. Similarly, Cloud et al. demonstrated an annual cost savings of $261,678 from decreased LOS and OR savings secondary to decreased need for temporary external fixation [22]. Following the implementation of a Saturday DOTR, Runner et al. calculated a $1.13 million per year savings due to decreased LOS [16]. Whitlock et al. also found cost savings from a dedicated fracture reduction room as well, with patients treated in the fracture reduction room accruing charges of $5,299 +/− $1,289 versus $10,455 +/− $2,290 in the OR (P < 0.001) [19]. In summary, significant cost reduction has been demonstrated with a DOTR/DOTL, however, the majority of studies did not report on this outcome measure.

4.7. Surgical complications

By providing traumatologists with ideal operating conditions, it was hypothesized that the availability of a DOTR would lead to decreased complications. Published literature regarding post-DOTR complications fall into many different categories, therefore, we opted to organize them as follows: mortality, unplanned reoperations, postoperative ICU admission, and miscellaneous complications.

4.7.1. Mortality

Of the 17 studies included in this review, 7 reported an outcome related to mortality. 2 out of 7 (29%) studies reported a statistically significant decrease in mortality, while 5 out of 7 (71%) studies reported no significant difference. No studies reported an increase in mortality. Chacko et al. published a report showing that the 1-year and 2-year mortalities of hip fracture patients were significantly less after the implementation of the DOTR, from 25% to 13% and 37% to 15%, respectively [13]. Similarly, Roberts et al. found a significant decrease in postoperative mortality in patients with femoral neck fractures following the development of a DOTR, from 5.6% before the DOTR to 0% after (P = 0.04) [14]. On the contrary, multiple studies noted no significant difference in the postoperative mortality [10,17,18,22,23].

Although the trend was evident for a decrease in the mortality associated with the respective procedures performed, the majority of the studies did not report a statistically significant change in the setting of a DOTR/DOTL.

4.7.2. Unplanned reoperation

Of the 17 studies included in this review, 2 reported an outcome related to unplanned reoperation. Both studies reported a decreased rate of unplanned reoperation following the implementation of a DOTR/DOTL. Brusalis et al. recorded a 53% reduction (P = 0.018) in unplanned reoperation for supracondylar humeral fractures after the implementation of a DOTR [9]. Similarly, Steeby et al. found an increased incidence of unplanned return to the OR for the on-call OR (42%) when compared to the DOTR (27.5%) (P = 0.018) [11]. While not analyzing the effects of a DOTR, Ricci et al. found that femoral or tibial shaft operations performed at night were twice as likely to require an unplanned reoperation (as discussed above) [6]. Although the trend was evident for a decrease in unplanned reoperation associated with the respective procedures performed, the majority of the studies did not study this outcome measure.

4.7.3. Postoperative ICU admission

Of the 17 studies included in this review, 2 reported an outcome related to postoperative ICU admission. Both studies reported a decreased rate of postoperative ICU admission following the implementation of a DOTR/DOTL. McDonald et al. found a statistically significant decrease (7.0% pre-DOTR vs 3.8% post-DOTR, P = 0.036) in hip fracture patients requiring postoperative ICU transfer following the development of a 6 am to 9 am DOTR [18]. Roberts et al. reports similar findings with a 9.3% decrease (P = 0.02) of postoperative ICU transfer for patients undergoing operative treatment of femoral neck fractures [14]. Although the trend was evident for a decrease in postoperative ICU admission, the majority of the studies did not study this outcome measure.

4.7.4. Miscellaneous complications

Steeby et al. found that following the implementation of a DOTR, primary fracture union was two times more likely when compared to the non-DOTR group for debridement of open tibia and femur fractures (P = 0.003) [11]. Lemos et al. also found that patients had significantly more complications before the implementation of the DOTR, including urinary tract infections, pressure sores, and cardiac complications (P < 0.001, P = 0.012, P = 0.046, respectively) [10]. Roberts et al. demonstrated a statistically significant decrease in any postoperative complication by 17% following the implementation of the DOTR (P = 0.04) [14]. Contradictorily, Cloud et al. demonstrated no statistically significant difference in complications including sepsis, surgical site infection, respiratory failure, or pulmonary embolism [22].

5. Limitations

A limitation of this review is the heterogeneity of the data collected among all the studies. There is variability in the published literature regarding the injuries and surgical methods analyzed and the model of DOTR/DOTL used by various institutions. In addition, the studies included in this review were retrospective and the majority included a before and after design. A major disadvantage of before and

after studies is that large changes can be made in processes and healthcare systems that affect outcomes, confounding the outcomes related to the specific intervention being studied [25]. As a result, there is a potential for a lack of generalizability of these findings. To account for this limitation, multiple studies have run mathematical and graphical simulations to determine situations in which a dedicated emergency operating room is advantageous. Importantly, these models were analyzing trauma of all specialties and often specifically excluded orthopaedic trauma [26]. Additionally, there was no distinction between emergent and urgent trauma, a foundational aspect of this review. Findings amongst these studies were split, with some favoring a dedicated room [27,28] while others favored dividing trauma amongst elective ORs [29]. Bowers et al. developed a simulation specifically for orthopaedic trauma and found that the utilization of trauma rooms can be increased by scheduling elective cases within the "dedicated" trauma time [30]. However, this model did report any morbidity or mortality outcomes related to potential delays in delivery of trauma care.

6. Conclusions

This review suggests that DOTRs/DOTLs have favorable effects on after-hours procedures, cost, and surgical complications. There is variability among the data regarding the effect on TTS, DOS, and LOS.

7. Interpretation

There is evidence to suggest that the DOTR/DOTL is beneficial in many regards for the orthopaedic patient, the orthopaedic surgeon, and in cost savings for the hospital. However, more research must be done to study the effects of the DOTR/DOTL on scheduling for other surgical specialties.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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