Trauma Monthly 2023; 28(3): 805-814

10.30491/tm.2023.394942.1591

Trauma Monthly

Original Article

Oral Levothyroxine Prophylactic Administration on Bleeding and Hemoglobin Changes During and after Total Hip Arthroplasty in Patients with a History of Ischemic Heart Disease: A Randomized Clinical Trial

Mehrdad Zamani Esfahlani [1], Mohammad Irajian [2], Misagh Osquee Asanjani [2], Hassan Mohammadipour Anvari [3*]

[1] Assistant Professor of Spine Surgery, Department of Orthopedics, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[2] Assistant Professor of Orthopaedics, Department of Orthopedics, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[3] Associate Professor of Anesthesiology, Department of Anesthesiology and Operating Room, School of Allied Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

*** Corresponding Author:** Hassan Mohammadipour Anvari, Associate Professor of Anesthesiology, Department of Anesthesiology and Operating Room, School of Allied Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran., ORCID: 0000-0003-3998-1275, Tel: +989188112210, Email: dr.anvaritbzmed@yahoo.com.

Received 2023-04-30; **Accepted** 2023-06-20; **Online Published** 2023-06-30

Abstract

Introduction: The reduction of thyroid hormones during surgery can affect the amount of bleeding. This study aimed to evaluate the effects of prophylactic administration of oral levothyroxine on bleeding and hemoglobin levels during and after THA in patients with a history of IHD.

Methods: In this double-blinded clinical trial, 40 THA candidates with a history of IHD were randomly divided into intervention and control groups. Twelve hours before the induction of anesthesia, patients in the intervention group received 20 µg levothyroxine, and patients in the placebo group received the same amount (one-fifth of a tablet) of a placebo. Also, during surgery, one tablet containing either 100 mg levothyroxine or a placebo was dissolved in 30 ml of water, and 20% of it was fed to the patients by gavage. One, two, three, and 12 hours after surgery, as well as on days 1st, 2nd, and 4th post-surgery, the same amount of the drug was given to the patients. Changes in hemoglobin level, bleeding volume (during and after surgery), and the number of blood units received were compared between the two groups.

Results: Red blood cell count (RBC) (intervention: P=0.855 and control: P=0.214), hemoglobin level (intervention: P=0.673 and control: P=0.123), and hematocrit (intervention: P=0.666 and control: P=0.096) were more stable in the intervention than in the control group. Also, bleeding volume was considerably lower in the intervention group (P=0.339) than in the control group (P=0.032). Also, serum volume in the operation room (P=0.019) and post-surgery (P=0.041) and the number of packed cell units received in the operation room (P=0.014) and after surgery (P=0.041) were significantly lower in the intervention group than in the control group.

Conclusion: The prophylactic administration of oral levothyroxine reduced bleeding volume and the need for blood transfusion and rendered blood indices (Hb, HCT, RBC, PT, and APPT) more stable in THA candidates with a history of IHD.

Keywords: Bleeding, Hemoglobin, Total hip arthroplasty, Cardiovascular diseases.

Introduction

Among the common and perilous consequences of bleeding during major surgeries [1], including total hip arthroplasty (THA), are the fluctuations of the serum levels of thyroid hormones, known as sick euthyroid syndrome (SES) [2]. Particularly, this phenomenon pertains to major surgeries [3]. During the surgery and over time, the serum level of T3 decreases slowly, and this reduction is expedited 90 minutes after introducing the surgical incision [4]. Some studies have noted that

severe hemodynamic changes after 90 minutes from the onset of surgery are caused by fluctuations in the levels of thyroid hormones [5], suggesting that supplementation with T3 can improve the hemodynamic balance and reduce the rate of bleeding [6]. However, this hypothesis requires more research to be approved [7].

Thyroid hormones affect the body's homeostatic balance, and thyroid disorders can trigger a wide spectrum of hemostatic abnormalities ranging from asymptomatic derangement of laboratory parameters to extensive bleeding or thrombosis [8-10]. Therefore, thyroid hormones can be crucial in maintaining the hemostatic balance in people undergoing major surgeries associated with extensive bleeding and modulating adverse effects on essential laboratory indicators and surgery outcomes [11, 12].

Levothyroxine is one of the drugs used to treat those suffering from hypothyroidism [13]. Three hours after oral consumption, this drug causes an increase in the serum level of the T4 hormone, which in turn is converted to T3 by mono-deiodinase in tissues, then enters cells through binding to its specific receptors and promotes its wide-range biological effects [14]. Several studies investigating the effects of thyroid hormone replacement therapy on candidates for major surgeries have affirmed the effectiveness of levothyroxine in reducing bleeding during these procedures [15-17]. On the contrary, several studies have pointed out that the prophylactic administration of levothyroxine cannot minimize bleeding during surgery [18]. Collectively, the effectiveness of this drug in reducing bleeding during and after major surgery is still unclear, highlighting the need for conducting more studies to clarify this issue [19].

As noted, bleeding during THA surgery can adversely affect the surgery outcomes [20]. On the other hand, candidates for THA often suffer from concurrent cardiac diseases [21]. Also, bleeding can aggravate the prognosis of people with a history of cardiac disorders and increase their post-surgery mortality and morbidities [22]. Considering that a reduction in thyroid hormones during surgery can contribute to the rate of bleeding and the fact that findings in this area are controversial, we aimed to investigate the effects of the prophylactic administration of oral levothyroxine on bleeding volume and hemoglobin levels in patients with a history of ischemic heart disease (IHD) during and after THA.

Methods

Study Design: This double-blinded randomized clinical trial was conducted on 40 THA candidates with a history of IHD in the Shohada and Imam Reza hospitals in Tabriz, Iran, between May 22, 2021, and April 22, 2021.

Sample Size Calculation and Sample Recruitment: Regarding the results of a similar study reporting [18] the volume of bleeding as 290.45±56.18 ml in the group of patients receiving levothyroxine and as 415.65±89.40 ml in the control group, using the formula designed for determining the sample size based on a quantitative outcome and considering an alpha error equal to 0.05 and the test power of 80%, the sample size for each group was determined as n=17. Considering a drop-out rate of 15%, the sample size in each group was considered to be n=20 people. Finally, 40 subjects were purposefully selected by the accessible sampling method.

Inclusion and Exclusion Criteria: The inclusion criteria in this study encompassed being a candidate for THA, age between 20 and 60 years, ASAI-II anesthesia class, elective surgery, having a history of IHD, and consent to participate in the study. Exclusion criteria were concurrent suffering from thyroid disorders, a history of taking amiodarone, serum creatinine level exceeding 1.5 mg/dl, experiencing myocardial ischemia within the last three months, suffering from bleeding disorders or coagulopathies, being allergic to levothyroxine, diagnosis of COPD, history of hemophilia, receiving blood products during the week before entering the study, consuming warfarin, presenting with systemic disorders, body mass index greater than 40 kg/m2, and receiving head and neck radiotherapy during the last three months.

Randomization: The patients were assigned to one of two study groups using the block randomization method. For this purpose, ten blocks (five blocks with a size of four for each study group) were used, and each block covered equal numbers of subjects in the two groups. The order of the blocks was determined by lottery, and based on being placed in what block, the patients were divided into either the intervention or control group.

Blinding: The researcher recording the data and outcomes in the data collection form must be aware of patient grouping. The data obtained were subsequently

delivered to a statistician outside the research group for analysis, who was also unaware of the grouping. Therefore, the present study had a double-blind design.

Study Protocol: Patients in the intervention group received 20 µg (one-fifth of a 100 µg tablet) of levothyroxine manufactured by Iran Hormone Pharmaceutical Company (Iran) 12 hours before the induction of anesthesia. The patients in the control group received the same amount of the drug as a placebo, mimicking the original drug in shape, size, and color. During surgery, one 100 mg tablet of either levothyroxine or placebo was dissolved in 30 mL of water, 20% of which was then fed to the patients by gavage. The same drug dose was administered to the patients at 1, 2, 3, and 12 hours' post-surgery and on days 1st, 2nd, and 4th after surgery. The need for blood transfusion was recorded in the two groups. It should be noted that if the patient required blood transfusion during surgery, hemoglobin level was measured beforehand to adjust the impact of transfusion on hemoglobin fluctuations within the following hour. The volume of serum received by each patient was also recorded. After anesthesia and intubation, a urinary catheter was installed for all patients to measure urine volume; initial urine was discarded so that the final urine volume could be accurately measured. Blood loss was estimated by measuring the volume of the drain after being emptied to determine bleeding volume accurately.

Bleeding volume measurement: The volume of blood loss in these patients was calculated visually based on the number of blood-soaked gauzes and the volume of blood in suction as follows. The number of 4-inch × 4-inch gauzes covered with blood and the volume of blood suctioned during surgery were recorded for each patient. Each 4-inch x 4-inch gauze contains 10 mL of blood, so the number of blood-covered gauzes was multiplied by 10, and the resultant value was combined with the volume of suctioned blood. Since the value obtained in this method also considers the volume of the fluids used for washing the surgery area, the volume of these fluids was deducted to achieve the proper volume of blood loss for every patient. It should be noted that all patients underwent general anesthesia using the same protocol and drugs.

Data collection: The information recorded for each patient in the data collection form included: age, body mass index, gender, ASA class, surgery side, duration of anesthesia, and duration of surgery. The parameters of red blood cell count (RBC), hemoglobin (Hb) level, and hematocrit (HCT) were measured before surgery, 1-, 2-, 3-, and 12-h, and one, two, and four days after the surgery. Also, Prothrombin Time (PT), Activated partial Prothrombin Time (PTT), the level of T3 hormone, bleeding volume at the specified times, the volume of serum received, changes in urine volume, and the number of blood units transfused were recorded before and after surgery.

Statistical analysis

One of the researchers, unaware of patient grouping, recorded information on data collection forms. After completing the data gathering, these forms were delivered to a statistician who was not a research team member. The mean ± standard deviation and frequency (%) were used to present the data, and the Mann–Whitney U, Chi-square test, and Friedman were used to compare within- and between-group variations. A P value of less than 0.05 was considered a statistically significant cut-off.

Results

During the mentioned period, there were 61 patients, of which 40 were included in the study and were present until the end of the study; In other words, the sample drop in this study was equal to 0(Chart 1). The mean ± standard deviation of the age and BMI of the participants were 55.49 ± 3.58 years and 29.14 ± 2.96 Kg/m2, respectively. Most participants were men (n=31) and underwent Class II anesthesia (n=28). The surgery on 24 subjects was performed on the right side; the average durations of surgery and anesthesia were 154.74±25.59 and 185.69 ±32.41 minutes, respectively. The comparison of the baseline variables revealed no statistically significant difference between the two groups (P>0.05, Table 1).

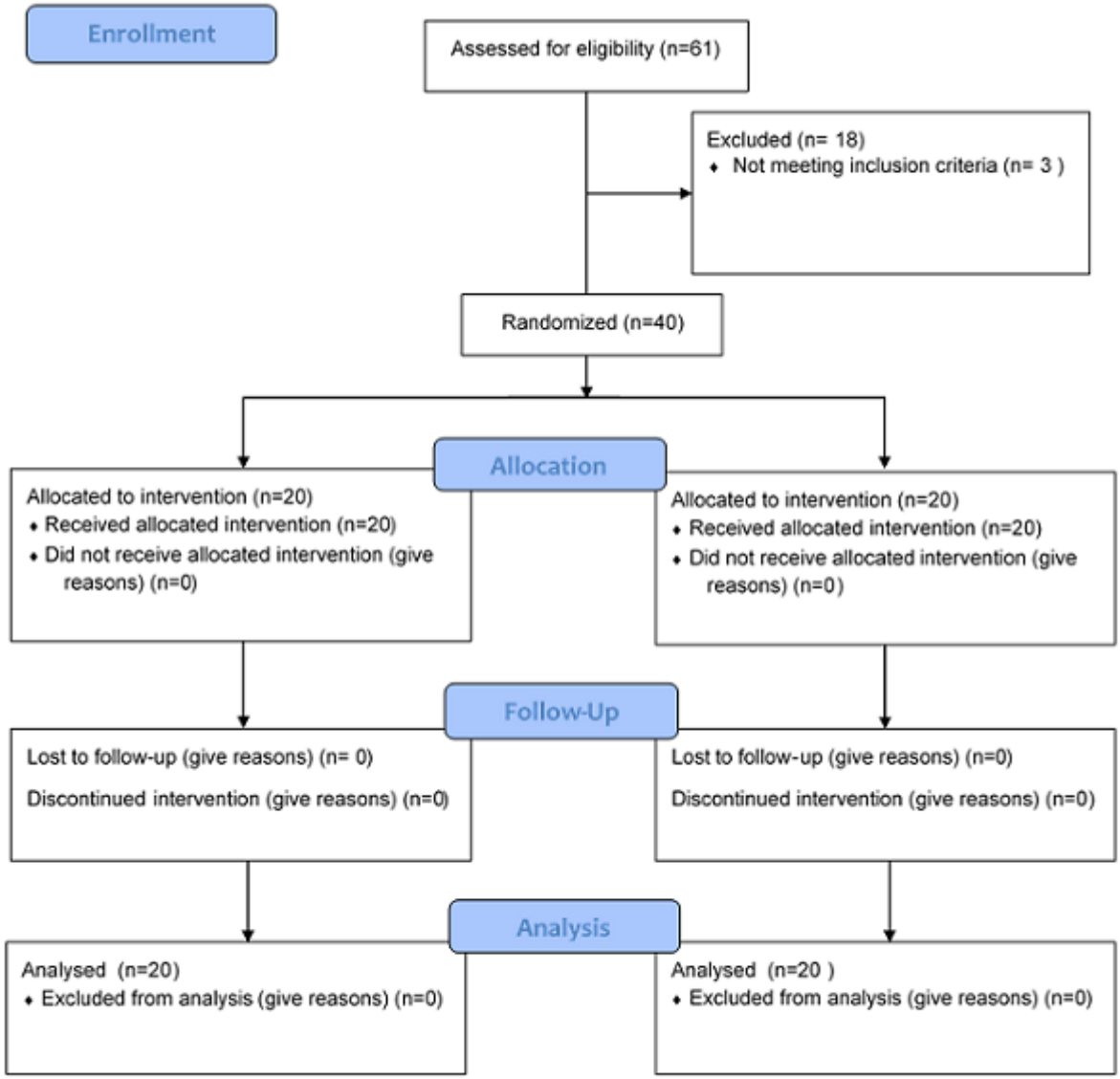

Figure 1: Outflow of patients in the study.

Table 1: Comparison of the Participants' Baseline Features.

Variables		Study groups (N=40)		P value
		Control group (N=20)	Intervention group (N=20)	
Age *		55.12±3.22	56.01±3.89	0.751
BMI *		28.73±2.45	29.85±2.63	0.656
Duration of surgery (min) *		151.44±24.75	158.56±27.20	0.883
Duration of anesthesia (min) *		180.67±30.25	191.14±35.57	0.856
Gender **	Male	16(80%)	15(75%)	0.896
	Female	4(20%)	5(25%)	
ASA class **	I	6(30%)	6(30%)	0.999
	II	14(70%)	14(70%)	
Surgery side **	Right	11(55%)	13(65%)	0.581
	Left	9(45%)	7(35%)	
*; Mann–Whitney U, **; Chi-square				

The comparison of blood parameters indicated no significant difference between the two groups regarding the baseline RBC. However, the RBC index on the first-day post-surgery, but not at other time points after the surgery, was significantly higher in the intervention group than in the control group (P <0.05). Also, RBC stability was higher in the intervention group (P=0.855) than in the control group (P=0.214). Although the baseline hemoglobin level was comparable between the two groups, this parameter was significantly higher in the intervention group than in the control group at all other time points (P <0.05). Also, fluctuations in hemoglobin levels were milder in the intervention group (P=0.673) than in the control group (P=0.123).

There was no significant difference between the two groups regarding the baseline Hct level; however, this parameter was significantly higher in the patients of the intervention group compared to their counterparts in the control group at all other time points. Also, the Hct level was more stable in the intervention group (P=0.666) than in the control group (P=0.096, Table 2).

The two groups had no significant differences regarding baseline PT, APTT, and T3 level. At the same time, all these parameters were significantly higher in the intervention group than in the control group at all times after the surgery (Table 3).

Comparing bleeding volume at different time points indicated a lower rate of bleeding in the intervention group (P=0.339) compared to the control group (P=0.032). Moreover, regarding the volume of serum received in the operation room (P=0.019) and after surgery (P=0.041) and the number of blood units transfused in the operation room (P=0.014) and after surgery (P=0.041), the participants in the intervention group showed significantly more stability compared to patients in the control group. This can be explained by the fact that requirements for serum and blood transfusion are influenced by bleeding volume, and because the average volume of bleeding was higher in the control subjects (P<0.05), they also required larger volumes of serum and packed cells compared to participants in the intervention group. There was a statistically significant difference between the two groups regarding the volume of urine as measured by the amount of urine collected in urination bags, indicating a significantly higher urine volume in the intervention group compared to the control group (Table 4).

Table 2: Comparison of Blood Parameters Between Participants in the Two Study Groups at Different Time points.

Variables		Study group (N=40)		P Value *
		Control group (N=20)	Intervention group (N=20)	
RBC	Baseline	6.49±1.19	6.32±1.89	0.751
	1-hour post-surgery	5.65±1.19	6.01±1.56	0.043
	3-hour post-surgery	5.03±1.19	5.88±1.24	0.044
	12-hour post-surgery	4.63±1.19	5.45±1.75	0.037
	Day 1st post-surgery	4.03±1.19	5.21±1.58	0.009
	Day 2nd post-surgery	4.59±1.19	5.03±1.66	0.312
	Day 4th post-surgery	4.66±1.19	4.88±1.37	0.588
	P value **	0.214	0.855	
Hb	Baseline	14.16±1.09	14.29±1.18	0.369
	1-hour post-surgery	12.24±1.48	13.55±1.45	0.009
	3-hour post-surgery	11.00±1.24	12.01±1.23	0.016
	12-hour post-surgery	10.91±1.41	12.41±1.33	0.039
	Day 1st post-surgery	10.85±1.29	12.35±1.26	0.041
	Day 2nd post-surgery	11.41±1.51	12.31±1.22	0.044
	Day 4th post-surgery	11.51±1.41	12.31±1.15	0.029
	P value **	0.123	0.673	
HCT	Baseline	41.41±1.51	39.57±6.77	0.707
	1-hour post-surgery	30.41±1.51	35.14±5.64	0.049
	3-hour post-surgery	26.41±1.51	33.12±5.39	0.015
	12-hour post-surgery	20.41±1.51	30.75±3.96	0.019
	Day 1st post-surgery	24.41±1.51	32.69±4.86	0.014
	Day 2nd post-surgery	25.41±1.51	30.66±5.73	0.049
	Day 4th post-surgery	26.41±1.51	32.34±5.33	0.041
	P value **	0.666	0.096	
*; Mann–Whitney U, **; Friedman Test				

Table 3: Comparison of PT, APPT, and T3 Level Between the Two Study Groups at Different Time points.

Variables		Study group (N=40)		P Value *
		Control group (N=20)	Intervention group (N=20)	
PT	Baseline	12.12±2.22	12.24±2.18	0.883
	After surgery	16.96±4.24	13.49±2.45	0.041
	P value	0.032	0.789	
APT T	Baseline	28.35±2.88	29.14±2.85	0.774
	After surgery	36.85±5.60	31.44±3.69	0.044
	P value *	0.029	0.793	
T3	Baseline	1.36±0.21	1.31±0.15	0.213
	After surgery	0.95±0.33	1.19±0.18	0.011
	P value *	0.001	0.103	
*; Mann–Whitney U				

Table 4: Comparison of Bleeding Volume, Serum and Blood Transfused, and Urine Volume Between the Participants in the Two Study Groups.

Variables		Study group (N=40)		P Value*
		Control group (N=20)	Intervention group (N=20)	
Bleeding	1-hour after performing the surgical incision	459.47±41.48	351.49±30.83	0.006
	3-hour after performing the surgical incision	451.34±41.59	281.59±45.11	0.005
	12 hours after performing the surgical incision	125.41±10.63	85.10±6.65	0.031
	Day 1st post-surgery	100.25±19.63	62.55±5.98	0.039
	Day 2nd post-surgery	50.48±3.65	0	0.014
	Day 4th post-surgery	0	0	0.999
	P value **	0.032	0.339	
Blood products transfused	During surgery	2.11±0.29	0.85±0.15	0.014
	After surgery	1.11±1.58	0.29±0.75	0.041
IV solutions received	During surgery	4.37±1.39	2.47±0.44	0.019
	After surgery	5.89±2.22	3.49±0.75	0.041
Urine volume in collection bag (mL)*		4523.74±856.61	2574.88±369.88	0.033
*; Mann–Whitney U, **; Friedman Test				

Discussion

Poor cardiac function is one of the causes of death in patients undergoing major surgeries [21]. Therefore, improving these patients' hemodynamic status and cardiac function during and after surgery is essential [22]. Regarding the key role of thyroid hormones in regulating the function of the cardiovascular system [23], the present study's objective was to investigate the effect of levothyroxine oral administration on the rate of bleeding in patients with a history of IHD undergoing THA. Individuals with a positive history of IHD are more likely to bleed during major surgeries than others, as they routinely take anticoagulants [24]. Thus, bleeding in

these people, whose hearts are generally weaker than usual, can cause them to develop irreversible cardiac damage. The results of the present study indicated that the parameters measured, including RBC, hemoglobin, and hematocrit, were more stable in the intervention group than in the control group. Also, the volume of bleeding, the serum volumes received in the operation room and after surgery, and blood units transfused in the operation room and after surgery were significantly lower in the intervention group compared to the control group [25-27].

According to the results of the present study, the mean concentration of serum T3 decreased in both groups, comparing pre-surgery and 12-h post-surgery levels; however, this reduction was statistically significant only in the control group, reflecting the positive role of prophylactic administration of oral levothyroxine in stabilizing serum levels of T3 hormone after surgery. Also, the two groups showed significant differences in the mean hemoglobin level, rate of bleeding, and requirement for blood products. According to these observations, prophylactic oral levothyroxine at the dose used in this study can have a beneficial role in reducing bleeding during and after surgery in patients undergoing THA. Several studies have investigated the effects of oral and intravenous administration of T3 on the hemodynamic status of patients undergoing various cardiac surgeries [28-30].

Various studies have scrutinized the effects of thyroid hormones on bleeding tendency and the function of the homeostatic system. In a study on patients undergoing bariatric surgery, low levels of thyroid hormones were concluded not to affect the risk of major bleeding in patients. Also, a case report indicated that the intravenous administration of thyroid hormones in an individual suffering from hypothyroidism presenting with gastrointestinal bleeding resistant to various endoscopic and non-thyroid hormone replacement treatments ceased bleeding and prevented its recurrence in the patient [30-33].

Different studies have reported variable effects of thyroid hormone replacement therapy in patients undergoing various surgeries. This can be attributed to differences in drug duration and dose, variable monitoring periods, and populations investigated. Considering these contradictory findings, thyroid hormones are yet to be embraced as drugs to improve the cardiac function of patients with heart abnormalities undergoing major surgeries [14, 19,21].

The present study has some limitations, including the small sample size, the short duration of patient monitoring, and the not measuring other functional thyroid hormones after drug consumption (according to previous studies, these hormones would remain unchanged). Therefore, conducting more studies with larger sample sizes and monitoring patients for extended periods is necessary. Also, considering that using levothyroxine in major surgeries is unprecedented, it is recommended to conduct more studies on the effects of different doses of levothyroxine on various functional indicators in larger populations.

Conclusion

The prophylactic administration of oral levothyroxine decreases the rate of bleeding and the need for blood transfusion. It renders hematological parameters (Hb, HCT, RBC, PT, and APPT) more stable in THA candidates presenting a history of IHD.

Acknowledgments

The authors of this article are grateful for the financial support of Tabriz University of Medical Sciences and the cooperation of the patients participating in the study.

Conflict of Interest Disclosures

None.

Funding Sources

This article is financially supported by the research vice-chancellor of Tabriz University of Medical Sciences.

Authors' Contributions

Article preparation (MI and HMA)
Study design (HMA and MZ)
Intervention (HMA, MOA and MZ)
Intervention follow-up (MZ, HMA and MAO)

Ethical considerations

The present study acquired ethical approval from the Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.REC. 1400.058) and was registered at the Iranian Registry for Clinical Trials (IRCT20180228038900N3). All the participants in this study signed an informed consent form after being briefed on the research objectives by the first author. None of the patients were deprived of routine treatments or charged extra fees for the tests performed in this study.

References

1. Kurtz S., et al. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. JBJS. 2005;87(7):1487–1497.

2. Holt J.B., et al. Minimizing blood transfusion in total hip and knee arthroplasty through a multimodal approach. The Journal of arthroplasty. 2016;31(2):378–382.

3. Rostami F, Osquee HO, Mahdavi F, Dousti S. Development of a new psychometric assessment tool for predicting hepatitis B virus infection in pregnant women. Int J Women's Health Reprod Sci. 2020;8(3):297-302.

4. Rosencher N., et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion. 2003;43(4):459–469.

5. Rezaei S, Naghipour B, Rezaei M, Dadashzadeh M, Sadeghi S. Chemical evaluation of gastrointestinal, coronary and pulmonary complications in patients admitted to the intensive care unit. Eurasian Chemical Communications.2022. 4(6): 557-566.

6. Ghojazadeh M, Paknezhad SP, Mohammadzadeh S, Rezaee M, Soleimanpour H. Dexmedetomidine for Procedural Sedation in the Emergency Department: A Systematic Review. Shiraz E Medical Journal.2022. 23(1):e113099.

7. Mahdavi F, Owaysee Osquee H. Comparison of serum levels of vitamin D after mastectomy in women with and without postoperative infection: case-control study. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2020;23(3):33-8.

8. Browne J.A., et al. Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. The Journal of arthroplasty. 2013;28(8):34–37.

9. Rezaee M, Ilkhchi NS, Zeinalzadeh M, Alvandfar D. The incidence of the symptoms of deep vein thrombosis in general anesthesia and spinal anesthesia after abdominal hysterectomy. Iranian Journal of Obstetrics, Gynecology and Infertility, 24(11).2021:45-51.

10. Park J.H., et al. Predictors of perioperative blood loss in total joint arthroplasty. JBJS. 2013;95(19):1777–1783.

11. Paulitsch FS, Schneider D, Sobel BE, Rached R, Ramires J, Jatene F, et al. Hemostatic changes and clinical sequelae after on-pump compared with offpump coronary artery bypass surgery: A prospective randomized study. Coron Artery Dis 2009; 20(2): 100-5.

12. Mobed A, Shirafkan M, Charsouei S, Sadeghzadeh J, Ahmadalipour A. Biosensors technology for anti-epileptic drugs. Clinica Chimica Acta. 2022. 533; 175-182.

13. Charsouei S, Esfahlani MZ, Dorosti A, Zamiri RE. Effects of COVID-19 pandemic on perceived stress, quality of life, and coping strategies of women with breast cancer with spinal metastasis under chemotherapy. International Journal of Women's Health and Reproduction Sciences.2021; 9(1):55-60.

14. Rousta F, Dadashzadeh M, Mahdavi F, Nasseri AR. Lymph Node Involvement and Related Risk Factors in Patients with Breast Cancer Referred for Radiotherapy: A 20-Year Study on 15 000 Women. International Journal of Women's Health & Reproduction Sciences. 2021;9(3):212-16.

15. Cerillo AG, Sabatino L, Bevilacqua S, Farneti PA, Scarlattini M, Forini F, et al. Nonthyroidal illness syndrome in off-pump coronary artery bypass grafting. Ann Thorac Surg 2003; 75(1): 82-7.

16. Ranasinghe AM, Bonser RS. Thyroid hormone in cardiac surgery. Vascul Pharmacol 2010; 52(3-4): 131-7.

17. Mohaddes G, Abdolalizadeh J, Babri S, Abedini N, Hossienzadeh F. The Anti-Edematous Effect of Ghrelin in Brain Hypoxia is Associated with Decreasing Expression of Vascular Endothelial Growth Factor. Journal of Molecular Neuroscience.2015; 56(2):273-277.

18. Atashkhoei S, Abedini N, Pourfathi H, Znoz AB, Marandi PH. Baricity of bupivacaine on maternal hemodynamics after spinal anesthesia for cesarean section: A randomized controlled trial. Iranian Journal of Medical Sciences.2017; 42(2):136-143.

19. Abedini N, Parish M, Farzin H, Pourfathi H, Akhsham M. The determination of an appropriate time for placement of the classic laryngeal mask airway in patients undergoing general anesthesia. Anesthesiology and Pain Medicine.2018; 8(2):e64427.

20. Timer E, Charsouei S, Bebek N, Baykan B, Bilgiз B, Sabancı PA, et al. Neurosurgical treatment of nonconvulsive status epilepticus due to focal cortical dysplasia. Epilepsy & behavior case reports. 2018; 10:4-7.

21. Hashemzadeh K, Dehdilani M, Gol MK. Study of the effects of simple exercise with or without physiotherapy on prevention of deep vein thrombosis among postmenopausal women requiring coronary artery bypass graft surgery. International Journal of Women's Health and Reproduction Sciences, 2021, 9(1): 69–74.

22. Hashemzadeh K, Dehdilani M, Gol MK. The effect of interval training on oxidative stress indices among women in preterm labor underwent coronary artery bypass graft. International Journal of Women's Health and Reproduction Sciences. 2020; 8(4):406–411.

23. Shanewise JS, Hines RL, Kaplan JA. Discontinuing cardiopulmonary bypass. In: Kaplan JA, editor. Kaplan's cardiac anesthesia. 5th ed. Philadelphia, PA: Elsevier Saunders; 2006. p. 1033.

24. Charsouei S, Esfahlani MZ, Dorosti A, Zamiri RE. Effects of COVID-19 pandemic on perceived stress, quality of life, and coping strategies of women with breast cancer with spinal metastasis under chemotherapy. Int J Women's Health Reprod Sci. 2021:55-60.

25. Ranasinghe AM, Quinn DW, Pagano D, Edwards N, Faroqui M, Graham TR, et al. Glucose-insulinpotassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. Circulation 2006; 114(1 Suppl): I245-50.

26. Haghdoost SM, Gol MK. The necessity of paying more attention to the neurological and psychological problems caused by covid-19 pandemic during pregnancy. International Journal of Women's Health and Reproduction Sciences. 2020; 8(3):243–244.

27. Kaptein EM, Sanchez A, Beale E, Chan LS. Clinical review: Thyroid hormone therapy for postoperative nonthyroidal illnesses: A systematic review and synthesis. J Clin Endocrinol Metab 2010; 95(10): 4526-34.

28. Spratt DI, Frohnauer M, Cyr-Alves H, Kramer RS, Lucas FL, Morton JR, et al. Physiological effects of nonthyroidal illness syndrome in patients after cardiac surgery. Am J Physiol Endocrinol Metab 2007; 293(1): E310-E315.

29. Squizzato A, Romualdi E, Buller HR, Gerdes VE. Clinical review: Thyroid dysfunction and effects on coagulation and fibrinolysis: A systematic review. J Clin Endocrinol Metab 2007; 92(7): 2415-20.

30. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: A prospective observational study. Transfusion 2008; 48(10): 2152-8.

31. Biondi B, Wartofsky L. Treatment with thyroid hormone. Endocr Rev 2014; 35(3): 433-512. 14. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the

treatment of hypothyroidism: Prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014; 24(12): 1670-751.

32. Malik FS, Mehra MR, Uber PA, Park MH, Scott RL, Van Meter CH. Intravenous thyroid hormone supplementation in heart failure with cardiogenic shock. J Card Fail 1999; 5(1): 31-7.

33. Choi YS, Kwak YL, Kim JC, Chun DH, Hong SW, Shim JK. Peri-operative oral triiodothyronine replacement therapy to prevent postoperative low triiodothyronine state following valvular heart surgery. Anaesthesia 2009; 64(8): 871-7.