SN Comprehensive Clinical Medicine (2023) 5:285
https://doi.org/10.1007/s42399-023-01620-y

ORIGINAL PAPER

# Evaluating the Effect of Oral Clonidine on Reducing Haemorrhage During Abdominal Hysterectomy

**Sheida Shabanian[1] · Labat Jafarzadeh[1] · Fatemeh Alavi[1] · Fatemeh Daris[2] · Bahram Khorram[3]**

Accepted: 20 November 2023 / Published online: 14 December 2023


## Abstract

Haemorrhage during surgery is one of the major complications of hysterectomy, making it necessary to use haemostasis agents to reduce haemorrhage. The present study is designed to determine the effect of the oral drug Clonidine on reducing haemorrhage during hysterectomy surgery. A double-blind clinical trial was conducted on 70 candidates admitted for abdominal hysterectomy. Patients were selected using the convenient sampling method and were randomly divided into two A and B groups which received Clonidine (0.2 mg) and placebo tablets, respectively. The tablets were prescribed 90 min before entering the operating room. The haemorrhage during surgery was obtained by counting the number of surgical gauges, and the level of haemoglobin and haematocrit in both groups before and 6 and 12 h after the hysterectomy. The data were then analysed using descriptive statistics and interracial statistics. The results showed that the haemoglobin and haematocrit of the intervention group were significantly higher than that of the control group 12 h after the intervention. The average haemorrhage during surgery was $308.29 \pm 58.99$ in the intervention and $339.43 \pm 56.10$ in the control group, which is significantly higher in the control group as compared to the intervention group ($P < 0.05$). The overall findings of the current study indicate the effectiveness of oral administration of Clonidine for reducing haemorrhage during hysterectomy surgery without resulting in significant side effects.

**Keywords** Clonidine · Haematocrit · Haemoglobin · Haemorrhage · Hysterectomy

## Introduction

Hysterectomy refers to the surgical removal of the uterus. Hysterectomy is often carried out by a gynaecologist and can be complete (including the removal of the main uterus mass, fundus, and cervix) or partial (removing the uterus whilst leaving the cervix untouched, also referred to as "Supracervical hysterectomy") [1]. Removal of the uterus will result in an inability to become pregnant whilst also creating a possibility for long-term complications. Therefore, this surgery is often only recommended when other treatment options are unavailable or have failed [2].

Hysterectomy is one of the major surgeries in women and is the second most common surgery in women after caesarean section. Statistics show that 37% of women in the USA and 20% in the United Kingdom will undergo a hysterectomy before the age of 60, with the majority of patients indicating the relief of symptoms caused by benign pathology and the resulting improved quality of life [3]. Hysterectomy, as a major surgery, affects the hormonal balance and overall health status of the patients. Therefore, a hysterectomy is often recommended as a last resort after trying drug treatments or other surgical interventions for the treatment of difficult uterus/reproductive system diseases. The common causes of hysterectomy include endometriosis, heavy abnormal uterine bleeding, uterine fibroids, uterine prolapse, prevention and treatment of uterine cancer, cancer in gynaecology, trans-male gender swap, severe developmental disorders, post-birth complications, and chronic pelvic pain [1, 2].

This article is part of the Topical Collection on Medicine.

✉ Fatemeh Alavi
drfatemehalavi2023@gmail.com

1 Clinical Research Development Unit, Department of Gynecology and Obstetrics, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran

2 Clinical Research Development Unit, Department of Epidemiology and Biostatistics, Shahrekord University of Medical Sciences, Shahrekord, Iran

3 Clinical Research Development Unit, Kashani Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran

The hysterectomy's complications can differ depending on the type of surgery and the techniques used. The most important complications include anaesthesia side effects, infection, venous thromboembolism, damage to the urinary-genital and digestive system, haemorrhage, and nerve damage. Other common complications in this surgery include sexual dysfunction, rupture of the vaginal cuff, and urinary incontinence [4]. Furthermore, anaesthesia and surgery complications as well as severe psychological problems due to the loss of the uterus and feminine identity are also observed in some patients [5]. The rate of death during hysterectomy is reported to be between 0.3 and 2 cases per 1000 cases in different centres, with the rate of death being higher in pregnant women or those suffering from cancer or other complications. Complications such as infection, haemorrhage, urinary and digestive complications, and pulmonary embolism can also be severe and result in patient death [6].

One of the most common complications in hysterectomy is haemorrhage during surgery [4]. The reported average blood loss volume during hysterectomy is different in various studies but an average of 500 mL of blood is lost during this elective surgery [7]. In general, various factors such as the length of surgery, the surgical method employed, surgical techniques, anaesthetise techniques, haemostasis, and the skill of the surgeon can affect blood loss during the surgery [8].

The blood loss during a hysterectomy can sometimes result in a need for blood transfusion, which is an invasive intervention with its side effects and complications including increased circulating volume, haemosiderosis, acute haemolytic reactions, septic shock, allergic reactions, and febrile nonhaemolytic reactions [9]. Controlled hypotension is one of the methods which can help reduce haemorrhage during surgery and improves the surgeon's visibility. Various medications are used for inducing hypotension including magnesium sulphate, vasodilators, nitro-glycerine, inhaled sedatives, beta-blockers, alpha-2 agonists, and Remifentanil [10].

Clonidine, which is also known by the trademark of Catapres, is an alpha-2 agonist which is used for the treatment of hypertension, ADHD, drug rehabilitation (for alcohol, opioids, or nicotine), hot flashes during menopause, diarrhoea, spasticity, and other conditions. This medicine reduces blood pressure and helps prevent stroke, heart attack, and renal disorders. Clonidine is also a mild sedative and can be used as a pre-surgery drug [11]. Clonidine reduces arterial blood pressure without reducing postural blood pressure whilst also reducing heart rate and haemorrhage during surgery whilst also decreasing the surgery time [12]. Studies have shown clonidine to be effective in reducing haemorrhage during rhinoplasty [13], transcanal endoscopic ear surgery [14], sinus endoscopic surgery [15], and spinal cord surgery [16].

The current study aims to evaluate the effect of oral clonidine on reducing Haemorrhage during a hysterectomy. To this end, the mean haemoglobin and haematocrit, mean haemorrhage during surgery, and the correlations with side effects (skin rash, drowsiness, low blood pressure, and headache) were investigated. In case of observed positive effects on reducing haemorrhage during surgery as well as low side effects, clonidine can be recommended as a suitable drug for reducing haemorrhage during hysterectomy surgery.

## Materials and Methods

### Study Design

The current study is a double-blind clinical trial that was conducted on 70 candidates for abdominal hysterectomy visiting Hajar Shahrekord Hospital. Table 1 shows the inclusion and exclusion criteria for patients in the current study.

**Table 1** Inclusion and exclusion criteria for the current study

| Inclusion criteria | Exclusion criteria |
|---|---|
| • The age range of 40 to 60 years old<br>• The patient's informed consent<br>• Lack of pregnancy<br>• Not using any antipregnancy medication 1 month before surgery<br>• Lack of history for systemic conditions and hereditary or acquired disorders<br>• Lack of history of using anticoagulant medications or drugs which can result in increased haemorrhage<br>• Lack of history of alcohol or drug abuse<br>• Lack of known allergy to clonidine<br>• Lack of history of abdominal surgery or abdominal adhesions<br>• Lack of using drugs which can result in reduced haemorrhage during surgery | • Requiring repeated surgery<br>• Opting out of the study or lack of cooperation during follow-ups<br>• Raynaud's syndrome, porphyria, or renal dysfunction<br>• Clonidine prescription counterindicators such as under 60 bradycardia or hypotension |

## Ethical Considerations

The following ethical considerations were used in the current study:

- Patients received sufficient explanation regarding the aims of the study and were asked for their informed consent for participation in the study.
- Patients were ensured regarding the confidentiality of their information.
- No additional costs were imposed on the patients.
- Furthermore, Clonidine has been used during rhinoplasty [13], transcanal endoscopic ear surgery [14], sinus endoscopic surgery [15], and spinal cord surgery [16] and no significant side effects were reported for the patients.

## Sampling

The sample size was calculated based on the effect size formula, the following equation, considering a 10% drop rate of 35 individuals per group.

$$n = \left( \frac{Z_{1-\frac{\alpha}{2}} - Z_{1-\beta}}{d} \right)^2$$
$$Z_{1-\frac{\alpha}{2}} = 1.96$$
$$Z_{1-\beta} = 0.84$$
$$d = 0.62$$

Before the surgery, demographic information (including age, the reason for the hysterectomy, history of anaemia, hypertension, diabetes mellitus, mental and psychological disorders, hypothyroidism, ischaemic heart disease, hyperlipidaemia, age, the total number of pregnancies, the total number of living and dead children, history of natural delivery and caesarean section, and medical and surgical records) were gathered for all patients.

## Intervention

The patients were hospitalized the day before the surgery and all patients underwent mechanical and chemical intestine preparation. Patients were under an NPO (nil per os) diet from 12:00 AM the night before surgery and each patient received 1 L of Ringer's lactate solution. All surgeries were carried out during the morning shift.

Patients were selected using the convenience sampling method and were randomly divided using Random Allocation software into two A and B groups which received Clonidine (0.2 mg) [15] and placebo tablets, respectively. The tablets were prescribed 90 min before entering the operating room. Furthermore, during the study, the surgical residents, surgical assistants, and statistical consultants were not informed about the drugs used for each group, and the tables were marked as A and B. The patients in both groups were equalized based on the anaesthesia drugs used and all patients underwent general anaesthesia. All surgeries were performed by one gynaecologist and one gynaecology resident. All surgeries were conducted using Pfannenstiel incision.

## Data Gathering and Analysis

Blood samples were taken from patients in both groups before and 6 and 12 h after the hysterectomy for haemoglobin and haematocrit measurement. The mean estimated blood loss during the surgery was obtained by using the Visual observation method [17, 18], from the sum of blood loss obtained from.

1. By counting the number of soaked gauges and volume of suctioned discharges during the surgery. In this regard, each gauge was fully soaked (equivalent to almost 10-cc blood loss), and each long surgical gauge was fully soaked (equivalent to almost 50-cc blood loss), and the volume of washing liquids was subtracted from the volume of the exposed blood. Although during the surgery the attempt was to expose gauges/loan to be fully soaked as much as possible; however, for those which were not fully soaked in blood, an equivalent of 5 cc blood was considered.
2. Determining the volume of drain secretions by observing the drain's markings and regarding the secretions 24 and 48 h after the surgery.

The side effects of Clonidine including skin rash, drowsiness, low blood pressure, and headache were also investigated for the intervention group. The information was entered into SPSS 18 software and analysed using descriptive statistics (mean, standard devising, frequency, and percentage) and inferential statistics (independent and paired *t*-test, repeated-measure ANOVA, and Chi-squared test). The significance level was less than 0.05 for all tests.

# Results and Discussion

In the current clinical trial, 70 candidates for abdominal hysterectomy visiting Hajar Shahrekord Hospital were included in the study and divided into two groups of 35 each, one receiving an oral dose of Clonidine (0.2 mg) and one receiving placebo tablets 90 min before the surgery. Both groups were almost identical in regards to the cause of hysterectomy, hypertension, diabetes mellitus, mental and psychological disorders, hypothyroidism, ischaemic heart disease, hyperlipidaemia, age, the total number of pregnancies, the

total number of living and dead children, history of natural delivery and caesarean section, mole, PSH, PMH, and PDH ($P<0.05$) but with differences in regards to the presence of anaemia and the total number of miscarriages ($P>0.05$) (Table 2).

According to the results of the ANOVA test, there was no significant difference between the mean haemoglobin of the two groups before the surgery ($P>0.05$) whilst there was a significant difference between the mean haemoglobin of the two groups at different times ($P<0.001$). The result of the Tukey post hoc test showed that the mean haemoglobin 6 h ($P<0.001$) and 12 h ($P<0.001$) after the intervention is significantly lower than before the intervention but that there is no significant difference between the values 6 and 12 h after intervention ($P>0.05$).

The mean haemoglobin at each time was significantly different between the two groups ($P<0.001$). The result of the Tukey post hoc test showed no significant difference in mean haemoglobin of the two groups before intervention ($P=0.563$) and 6 h after intervention ($P=0.070$) but that the mean haemoglobin of the intervention group is significantly higher than that of the control group 12 h after the intervention ($P=0.008$) (Tables 3 and 5 and Graph 1).

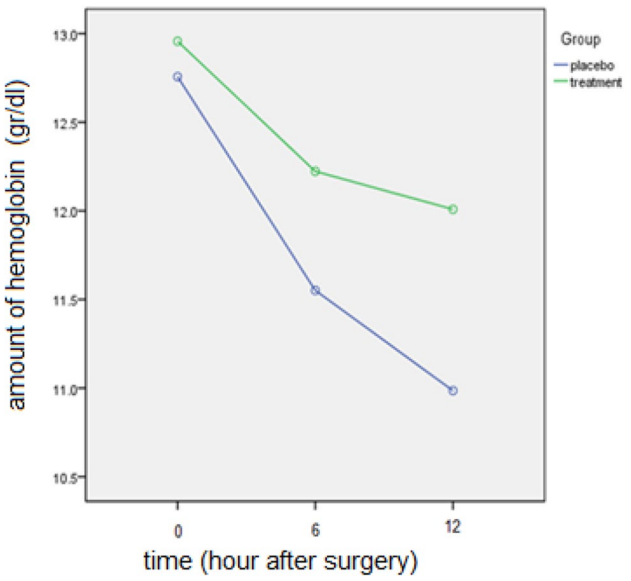
The repeated-measure ANOVA showed no significant difference between the mean haematocrit of the two groups ($P<0.05$) whilst there was a significant difference in mean

**Table 3** Descriptive haemoglobin indicators in control and intervention groups in the current study

| Time | Group | |
|---|---|---|
| | Control ($n=35$) | Intervention ($n=35$) |
| Before intervention | 12.76 ± 1.75 | 12.96 ± 1.04 |
| 6 h after the intervention | 11.55 ± 1.84 | 12.22 ± 1.11 |
| 12 h after intervention | 10.99 ± 1.66 | 12.01 ± 0.97 |

**Table 2** Comparison of demographic information between groups in the current study

| Demographic specifications | | Number in groups | | *P*-value |
|---|---|---|---|---|
| | | Control ($n=35$) | Intervention ($n=35$) | |
| Cause of hysterectomy | Abnormal uterine haemorrhage | 31 (88.6) | 26 (74.3) | |
| | Myomas | 4 (11.4) | 6 (17.1) | 0.239 |
| | Endometrial hyperplasia | 0 (0) | 1 (2.9) | |
| | Uterine prolapse | 0 (0) | 2 (5.7) | |
| Anaemia | No | 26 (74.3) | 33 (94.3) | 0.022 |
| | Yes | 9 (25.7) | 2 (5.7) | |
| Hypertension | No | 25 (71.4) | 26 (74.3) | 0.788 |
| | Yes | 10 (28.6) | 9 (25.7) | |
| Diabetes mellitus | No | 32 (91.4) | 34 (97.1) | 0.614 (f) |
| | Yes | 3 (8.6) | 1 (2.9) | |
| Mental and psychological disorders | No | 32 (91.4) | 33 (94.3) | 1.000 (f) |
| | Yes | 3 (8.6) | 2 (5.7) | |
| Hypothyroidism | No | 27 (77.1) | 32 (91.4) | 0.101 |
| | Yes | 8 (22.9) | 3 (8.6) | |
| Ischaemic heart disease (IHD) | No | 34 (97.1) | 33 (94.3) | 1.000 |
| | Yes | 1 (2.9) | 2 (5.7) | |
| Hyperlipidaemia (HLP) | No | 34 (97.1) | 32 (91.4) | 0.612 (f) |
| | Yes | 1 (2.9) | 3 (8.6) | |
| Age (years) | | 49.60 ± 5.15 | 50.06 ± 4.39 | 0.69 |
| Total pregnancies | | 4.51 ± 2.66 | 3.83 ± 2.14 | 0.239 |
| Total miscarriages | | 0.63 ± 1.03 | 0.20 ± 0.41 | 0.025 |
| Total living children | | 3.66 ± 2.07 | 3.31 ± 1.69 | 0.451 |
| Total dead children | | 0.26 ± 0.56 | 0.26 ± 0.66 | 1.000 |
| Mole | | 0.0 ± 0.0 | 0.06 ± 0.24 | 0.154 |
| Normal vaginal delivery (NVD) | | 3.31 ± 2.44 | 2.77 ± 2.46 | 0.357 |
| Caesarean section | | 0.57 ± 0.82 | 0.80 ± 0.76 | 0.229 |
| Previous surgery history (PSH) | | 0.89 ± 0.9 | 1.14 ± 0.85 | 0.222 |
| Previous medical history (PMH) | | 1.00 ± 1.03 | 0.63 ± 0.73 | 0.086 |
| Previous drug history (PDH) | | 1.00 ± 1.03 | 0.63 ± 0.73 | 0.086 |




**Graph 1** Descriptive indicators of haemoglobin for control and intervention groups at different times during the study

**Table 4** Descriptive haematocrit indicators in control and intervention groups in the current study

| Time | Group | |
|---|---|---|
| | Control ($n=35$) | Intervention ($n=35$) |
| Before intervention | 38.22 ± 5.22 | 38.82 ± 3.10 |
| 6 h after the intervention | 34.61 ± 5.49 | 36.71 ± 3.40 |
| 12 h after intervention | 33.92 ± 5.02 | 35.74 ± 3.49 |

haematocrit at different times ($P<0.001$). The Tukey post hoc test showed that the mean haematocrit value at 6 ($P<0.001$) and 12 h ($P<0.001$) after the intervention is significantly lower compared to before intervention but that there is no significant difference between 6 and 12 h after intervention ($P>0.05$).

Comparison of the mean haematocrit at each time between control and intervention groups shows a significant difference ($P<0.001$). Furthermore, the Tukey post hoc test showed that there is no significant difference between mean haematocrit in control and intervention groups before intervention ($P=0.561$) and after intervention ($P=0.060$) whilst the mean haematocrit of the intervention group is significantly higher than the control group receiving placebo 12 h after the intervention ($P=0.008$) (Tables 4 and 5 and Graph 2).

In regards to the post-operation complications, the majority of the participants did not require drain installation, PC, headache, drowsiness, or low blood pressure and no participant showed any rash. Furthermore, there was no significant correlation in post-operation complications between the two groups ($P>0.05$) (Table 6). Only one patient in each group required drain installation whilst 4 patients from the control group and 2 patients from the intervention group required blood transfusion (Table 6). The average haemorrhage during surgery was 308.29 ± 58.99 in the intervention and 339.43 ± 56.10 in the control group. The results of the independent *t*-test showed that the average haemorrhage during the surgery is significantly higher in the control group compared to the intervention group ($P=0.027<0.05$, $t=2.263$, df = 68).

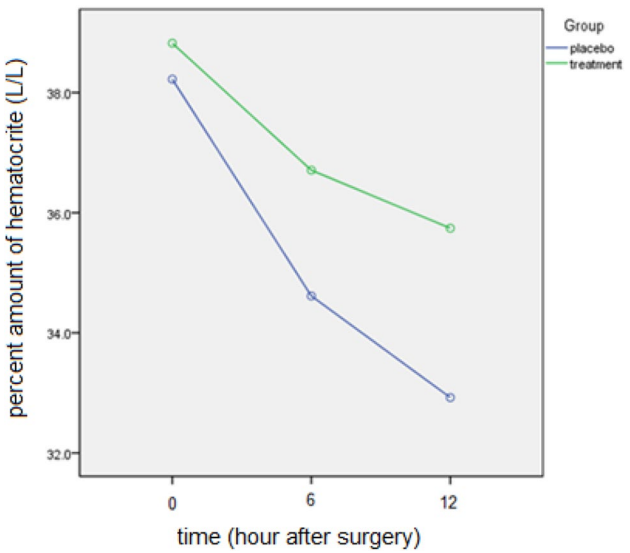
The statistical analyses showed that the mean haemoglobin and haematocrit showed no significant difference before and 6 h after the surgical intervention between Clonidine and placebo groups. However, 12 h after the surgery, the intervention group receiving Clonidine had a significantly higher value compared to the placebo group. Furthermore, the mean haemorrhage during surgery was 308.29 ± 58.99 mL in the intervention and 339.43 ± 56.10 mL in the control group, which shows a significant difference.

Clonidine is an alpha-2 adrenergic agonist which is generally used as an adjuvant anaesthetic drug due to its sedative and anaesthetic properties [19]. Furthermore, its desirable effects on patient haemodynamics for inducing hypotension are confirmed by anaesthesiologists [17]. Clonidine causes hypotension through a reduction of heart rate, relaxation of valence vessels, and reduction of peripheral vascular resistance. The induced hypotension during surgery can be effective in decreasing the haemorrhage during the surgery, improving the surgeon's vision, and preventing complications caused by haemorrhage [20].

The result of the current study also shows that there has been no significant difference between the groups receiving Clonidine and placebo in regards to drug side effects including requiring drain installation, requiring PC, headache, drowsiness, decreased blood pressure, and rash. This indicates the safety of Clonidine administration and can recommend its use for decreasing haemorrhage during hysterectomy, as shown also in other studies [19]. In this regard, in the study by Rao et al. in 2022 on patients undergoing

**Table 5** The repeated-measure ANOVA results for the effect of groups (intervention and control) and time (before intervention, and 6 and 12 h after intervention) as well as the effect of time for each group

| | Effect of group | | | Effect of time | | | Effect of time in each group | | |
|---|---|---|---|---|---|---|---|---|---|
| | *F* | *dF* | *P* | *F* | *dF* | *P* | *F* | *dF* | *P* |
| Haemoglobin | 3.555 | 1.68 | 0.064 | 199.418 | 2.136 | <0.001 | 17.329 | 2.136 | <0.001 |
| Haematocrit | 3.307 | 1.68 | 0.073 | 147.682 | 2.136 | <0.001 | 10.318 | 2.136 | <0.001 |




**Graph 2** Descriptive indicators of haematocrit for control and intervention groups at different times during the study

laparoscopy, observations indicate that the frequency of bradycardia and hypotension was 12.5% and 10% in the Clonidine group and 0% in the control group. Furthermore, none of the patients in the Clonidine group showed signs of nausea, vomiting, tachycardia, or hypertension whilst these side effects were observed in 17.5%, 17.5%, and 12.5% of cases in the control group, respectively [17]. In another study, Javaherfroosh et al. used 0.2-mg Clonidine tablets and observed that this resulted in a decrease in the occurrence of nausea and vomiting after surgery in the Clonidine group (observed in 21% and 16% of cases, respectively) compared to the control group (observed in 44% and 33% of cases, respectively) [19].

The overall findings of the current study are similar to previous studies [9, 10, 13–16, 20–25], indicating the effectiveness of oral administration of Clonidine for reducing haemorrhage during hysterectomy surgery without resulting in significant side effects. Therefore, Clonidine can be recommended as an effective and safe option for reducing haemorrhage during surgery. The advantages of the current study include using several methods for estimating the haemorrhage including counting bloodied surgical gauges, determining of haemorrhage based on drain volume, and measurement of haemoglobulin and haematocrit after the operation which improves the accuracy of the results. Furthermore, all surgeries were performed by one person to mitigate the effect of the surgeon's skills as the skill of the

**Table 6** The comparison between post-operation complications between the control and intervention group

| Complications | | Groups | | *P*-value |
|---|---|---|---|---|
| | | Control ($n=35$) | Intervention ($n=35$) | |
| Requiring drain installation | No | 34 (97.1) | 34 (97.1) | 1.000 (f) |
| | Yes | 1 (2.9) | 1 (2.9) | |
| Requiring PC | No | 31 (88.6) | 33 (94.3) | 0.673 (f) |
| | Yes | 4 (11.4) | 2 (5.7) | |
| Rash | No | 35 (100) | 35 (100) | – |
| | Yes | 0 (0) | 0 (0) | |
| Drowsiness | No | 21 (60) | 20 (57.1) | 0.808 |
| | Yes | 14 (40) | 15 (42.9) | |
| Headache | No | 32 (91.4) | 27 (77.1) | 0.101 |
| | Yes | 3 (8.6) | 8 (22.9) | |
| Low blood pressure | No | 35 (100) | 30 (85.7) | 0.054 (f) |
| | Yes | 0 (0) | 5 (14.3) | |
| Discharge in 24 h | 0 | 34 (97.1) | 34 (97.1) | 1.000 |
| | 30 | 0 (0) | 1 (2.9) | |
| | 60 | 1 (2.9) | 0 (0) | |
| Mean discharge | | $1.71 \pm 10.14$ | $0.86 \pm 5.07$ | 0.656 |
| Discharge in 48 h | 0 | 34 (97.1) | 34 (97.1) | 1.000 |
| | 70 | 0 (0) | 1 (2.9) | |
| | 90 | 1 (2.9) | 0 (0) | |
| Mean discharge | | $2.57 \pm 15.21$ | $2.00 \pm 11.83$ | 0.861 |
| Total PC | 0 | 31 (88.6) | 32 (94.03) | 0.673 (f) |
| | 1 | 3 (8.6) | 2 (5.7) | |
| | 2 | 1 (2.9) | 0 (0) | |
| Mean PC | | $0.14 \pm 0.43$ | $0.06 \pm 0.24$ | 0.305 |

surgeon can be a key factor in reducing the surgery and surgery results. The weakness of the current study is the small sample size and it is recommended that the study be repeated with a larger sample size and by measuring haemodynamic parameters.

## Conclusions

Based on the results of the current study, candidates for abdominal hysterectomy who had received oral Clonidine 90 min before the surgery showed significantly lower haemorrhage during the surgery compared to the placebo group, and their haemoglobulin and haematocrit levels, 6 and 12 h after surgery were significantly higher. Furthermore, there was no significant difference between the side effects between the two groups. Therefore, oral Clonidine can be used as an excellent pre-surgical medication, providing a safe and feasible method for reducing haemorrhage during surgery.

## Recommendations

- It is suggested that the effect of Clonidine be compared to that of other hypotension-induction drugs such as vasodilators, nitro-glycerine, inhaled decongestants, and beta-blockers for reducing haemorrhage during abdominal hysterectomy.
- It is recommended for future studies to investigate the effect of pre-surgery administration of Clonidine on other variables such as the use of anaesthesia drugs, arterial blood pressure, surgeon satisfaction, and the length of abdominal hysterectomy surgery.

**Acknowledgements** The authors would like to thank the Clinical Research Development Unit, Hajar Hospital, and Shahrekord University of Medical Sciences for their support, cooperation, and assistance throughout the period of study.

**Author Contribution** S. S.: design of the research procedure. L. J.: hysterectomy surgery supervisor. F. A.: hysterectomy surgery resident, collecting of data, writing — review and editing of the manuscript. F. D.: statistical analyser. B. K.: anaesthesiologist advisor. All authors have read and approved the final manuscript.

**Funding** None

**Data Availability** All data and materials are fully presented in the article.

**Code Availability** Not applicable.

## Declarations

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. IR.SKUMS. REC. 1400.178.

**Consent to Participate** Informed consent was obtained from all individual participants included in the study.

**Consent for Publication** Informed consent for publication was obtained from all individual participants included in the study.

**Conflict of Interest** The authors declare no competing interests.

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