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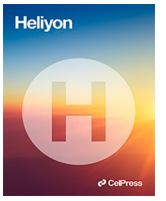

Investigation of the effects of intranasal desmopressin on the bleeding of the patients during open septorhinoplasty: A randomized double-blind clinical trial

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ABSTRACT

Objectives: Rhinoplasty is one of the most common cosmetic surgeries in the world. Lack of adequate local homeostasis may lead to excessive bleeding during the operation, which increases the time of operation and recovery period, and the prevalence of complications. This study investigated the effects of nasal desmopressin on the quality of the surgical field and the volume of bleeding during rhinoplasty.

Materials and methods: This double-blind randomized clinical trial was performed on 120 patients aged 18–40 years who were candidates for rhinoplasty. Patients were randomly divided into three groups: low-dose desmopressin group and high-dose desmopressin group and placebo group. Hemodynamic changes and surgical field based on BOEZAART criteria, and the volume of bleeding were calculated.

Results: In this study 115 women (95.8%) and 5 men (4.2%) participated. The mean age of patients was (27 ± 6.8). Bleeding volume in high dose desmopressin group was (21.7 cc ± 12.3), (27.7 cc ± 12.3) in low dose group, and (38.3 cc ± 12.3) in the placebo group, The difference in blood volume among the three groups was statistically significant with $p < 0.005$. Clean surgical field according to BOEZAART classification was marginally significant in both desmopressin groups. The differences in blood pressure, heart rate, blood and urine sodium, and hemoglobin before and after surgery between groups there not statistically significant.

Conclusion: Based on the results of the present study topical nasal spray desmopressin can reduce surgical field bleeding during rhinoplasty. To generalize the results to other surgeries in the ENT field it is recommended to conduct studies.

1. Introduction

As a surgical technique designed to address the both aesthetic and functional nasal concerns, septorhinoplasty has cemented its

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place within the modern and current field of otorhinolaryngology [1–3]. The annual number of these operations carried out in the United States is estimated to be between 250,000 and 300,000, underscoring the wide prevalence of the intervention [4,5]. This technique is an effective solution for rectifying anatomical abnormalities like a deviated septum, causing nasal airway obstruction [6], as well as enhancing nasal aesthetics (through cosmetic nasal surgery), significantly augmenting the quality of life for numerous patients who suffer from the nose-related anatomical abnormalities or search for the most effective cosmetic operations [5,7]. However, in spite of the fact that there are prominent positive clinical outcomes and substantial progress in the current surgical methodologies, septorhinoplasty does not come without potential risks and complications [1,2,8,9]. To be more precise, recurrent complications that are manifested during the operative and post-operative phases of septorhinoplasty, can be divided into two main categories, including traumatic cerebrospinal fluid leakage, and hemorrhage [1,2,4,6,8–10], and some unexpected and rare events like loss of vision [11]. These potential threats can adversely affect the duration and quality of the surgery, detrimentally diminish the visibility in the surgical field, and even compromise the patient's safety overall. Due to this bleeding, surgeons are expected to proficiently and skillfully manage the hemostasis, as well as intraoperative bleeding [9,12,13]. Results from several studies reported that roughly 15–20% of septorhinoplasty surgeries result in considerable bleeding complications, and the incidence of severe hemorrhage can significantly vary based on the individual patient's characteristics, as well as specific types of the applied surgical techniques [14]. This consistently-high rate of hemorrhage can result in a prolonged hospitalization, and an extortionate expenditures imposed on the healthcare system. It may also cause a significant psychological burden on the patients, affecting their in-hospital recovery time, recuperation, and post-operative satisfaction [9,15]. Taking the clinical implications and the hemorrhagic complications into account, it is blatantly evident that there is a clear and increasing demand for further investigations into the contributory factors and development of evidence-based medicine and clinical strategies for the better management of bleeding risks in septorhinoplasty surgeries. Hence, the necessity of devising and validating efficacious approaches to mitigate the hemorrhage in this context remains a primary research interest in the field [5,16].

A variety of strategies have been employed to minimize the intraoperative and post-operative bleeding rate in septorhinoplasty procedures, ranging from traditional interventions to the more innovative and effective techniques. Traditional strategies have primarily focused on the retaining hemostasis during septorhinoplasty surgery, often incorporating the usage of cautery, and post-operative packing of the nasal cavity, or the clinical usage of corticosteroids (like prednisolone) [17,18]. Despite their merits, these aforementioned conventional strategies come with their own set of drawbacks, such as discomfort during packing removal, and potential risks associated with the usage of cautery, including thermal injury to the surrounding tissues. In an attempt to address these problematic challenges, an upsurge in the research examining pharmacological interventions aimed at reducing the bleeding risks in septorhinoplasty procedures should not be underestimated. One of the ancient and widely-accepted approaches for reducing the bleeding rate in septorhinoplasty procedures was the usage of antifibrinolytic agents, such as tranexamic acid in the pediatric cleft palate surgeries, rhinoplasty, facial plastic surgeries, septo-plastic surgeries, and orthognathic surgeries [19–27]. Another solution was the usage of clonidine dexmedetomidine during functional endoscopic sinus surgeries [28–33], and endoscopic transsphenoidal pituitary surgeries [34], which have potentially and promisingly lessen the need for nasal packing and post-operative bleeding. However, the clinical applications of these aforesaid agents remain somewhat controversial due to the potential systemic side effects, including a theoretical increased risk for the thromboembolic events. More recently, a considerable attention has been shifted towards the clinical application of vasoconstrictive agents such as epinephrine [35]. These agents have been topically utilized, providing a localized vasoconstriction, and thereby leading to a reduced bleeding rate. Nonetheless, their limited duration of action and potential systemic effects should not be overlooked. According to these shortcomings, newer vasoconstrictive agents (including intranasal desmopressin) have practically come under the clinical investigations. Early studies have shown promising windows (more effective clinical outcomes in reducing the bleeding rate when compared to tranexamic acid [36]), however, further comprehensive research and more collaboration among the surgeons, anesthesiologists, and clinical pharmacologists are chiefly required to ascertain their efficacy and safety profiles in the context of septorhinoplasty especially in case of patients with von Willebrand diseases [37–39].

Desmopressin (1-deamino-8-D-arginine vasopressin), an analogue of the hormone vasopressin, has demonstrated the clinical potentials in promoting the hemostasis and reducing the bleeding rate in several clinical settings with an extended half-life [4,40,41]. Primarily, it acts by stimulating the release of some blood factors like von Willebrand Factor (vWF), tissue plasminogen, and factor VIII from the endothelial cells, thereby enhancing the coagulating activities through platelet adhesion and aggregation at the site of vascular injury, leading to a decreased partial thromboplastin activity, and a reduced bleeding time. The unique feature of desmopressin is it's ability to create a localized effect, focusing it's action specifically at the site of bleeding without affecting the systemic hemostasis [42–44]. Desmopressin selectively stimulates the function of vasopressin-2 receptor, and causes a transient reduction in the blood pressure in addition to the antidiuretic actions. In the context of septorhinoplasty, the potential clinical applications of intranasal desmopressin is of particular interest. Preliminary studies have shown that the clinical administration of desmopressin before surgery can significantly reduce the intraoperative bleeding, and the risk for edema and ecchymosis [45–47], leading to the increased quality of the surgical field during functional endoscopic sinus surgery [48,49], endoscopic transsphenoidal pituitary surgery [50], and Craniofacial or orthognathic surgical procedures [51]. The hemostatic effects of the intranasal and intravenous forms of desmopressin are of paramount importance in the inhibition of bleeding in hemophilic patients, and patients with von Willebrand disease (type 1). The intravenous application of desmopressin prior to facelift surgery was promisingly associated with a reduction in microhematoma formation [52]. These results suggest not only an improved safety profile for those patients, but also a potentially better visibility for the surgeon, facilitating a more precise operation and ultimately, a better surgical outcome. Furthermore, post-operative administration of desmopressin may also help minimizing the post-operative bleeding, one of the most concerning complications of septorhinoplasty, leading to a shorter hospital stay, reduced healthcare costs, and increased patient satisfaction [41,48]. Nevertheless, it is crucial to remember that while these primary findings are promising, more extensive and interdisciplinary research is required to

further elucidate the precise role and clinical efficacies of desmopressin administrated in septorhinoplasty. A better understanding of its impact on bleeding rate, hemorrhage, and the overall quality of surgery is crucial to inform evidence-based guideline and optimize patient's outcomes.

According to the low numbers of the studies investigating the clinical benefits acquired from topical administration of desmopressin aimed at reducing the hemorrhage rate in the patients undergoing septorhinoplasty, the current study aims to contribute to providing valuable, tangible, and evidence-based insights into the effects of intranasal administration of desmopressin on the intraoperative and post-operative the bleeding rate, hemorrhage, the quality of surgery (surgical field visibility), clinical outcomes of the patients when it was applied 1 h before an open septorhinoplasty. This study aims to add substantial depth to the current understanding of the role and utility of intranasal desmopressin, and is anchored in the premise that the better management of bleeding and hemorrhage can contribute significantly to the safety, efficiency, patient satisfaction, and overall success of the surgical procedure.

2. Material and methods

In this double-blinded randomized clinical trial conducted from 2021 to 2022, patients aged 18–40 years who were candidates for septorhinoplasty at Amiralmomenin Hospital, Guilan University of Medical Sciences (GUMS), Rasht, Iran, were incorporated. The study was sanctioned by the Ethics Committee of GUMS (IR.GUMS.REC.1399.505) and was in adherence to the Helsinki Declaration regulations. It was also registered in the Iranian Registry of Clinical Trials (IRCT; 20200708048051N3).

A sample size of 40 patients per group was calculated based on the G-power version 3.1.9.2, considering a 5% margin of safety and a 95% confidence interval. The average quality of the surgical field, based on Haddady's research (1), was 4.08 (0.62) for the desmopressin group and 4.59 (0.76) for the control group.

Patients with medical histories of cardiovascular diseases, coagulopathies, seizure disorders, cerebral diseases, hypertension, hyponatremia, and diabetes, those taking vitamin E or diuretics, and those who used corticosteroids within the last two weeks were not included in the study.

A week before surgery, the baseline hemoglobin, platelet count, serum and urine sodium, and coagulation test were examined. Hemoglobin and urine sodium were reevaluated one day after surgery.

In total, 120 patients were randomly divided into three groups after obtaining informed consent. The low-dose desmopressin group (LD-Des) received a single dose of nasal spray Desmex 10 μ/dose [Sina Darou Laboratories Company, Tehran, Iran] and a single dose of nasal spray 0.65% NaCl [Raha Pharmaceutical Company, Isfahan, Iran] per nostril (20 μg), in high-dose desmopressin group (HD-Des) double dose of nasal spray Desmex per nostril (40 μg) was administered, and, placebo group used double dose of nasal spray 0.65% NaCl per nostril.

Randomization was performed by means of PASS software version 11 (NCSS), implementing block randomization with a block size of six and the same allocation. Randomization and blinding were managed by a colleague who was outside the research team, and all research staff were blinded to the assignments.

One hour prior to surgery, group 1 received 1 puff of intranasal desmopressin and 1 puff of normal saline in each nostril (total 20 μg), group 2 received two puffs of topical desmopressin (total 40 μg), and group 3 received two puffs of intranasal normal saline. Each patient was provided with two coded bottles and instructed to spray one puff from each bottle on each side.

All patients underwent general anesthesia with total intravenous anesthesia (TIVA - midazolam 1 mg, propofol 2.5 mg/kg, lidocaine 20–40 mg, and *cis*-atracurium 0.1–0.2 mg/kg). Anesthesia maintenance was achieved with the administration of remifentanil 0.1 μg/kg/min and propofol 50–150 μg/kg/min. Mean Arterial Pressure (MAP) was kept within a range of 85–100 mmHg throughout the surgery.

The study aimed to ascertain the efficacy of differing doses of intranasal desmopressin versus placebo on intraoperative bleeding during septorhinoplasty. The main objectives were to quantify the blood loss volume and evaluate the quality of the surgical field. Intraoperative blood loss was measured using a suction bottle (accuracy: ±10 ml), and the surgical field quality was assessed based on the BOEZAART scale that is classified from 1 to 5 with increasing fashion, while, 1 stands for a dry field and 5 is a state of continuous bleeding. Mean arterial blood pressure and pulse rate were recorded every 15 min.

2.1. Statistical analysis of the data

STATA Statistics computer software for Windows version 14.0 (IBM Corp. released 2012. Armonk, NY, USA) was used for statistical analysis of the acquired data. To analyze the results, data were analyzed using descriptive tests reported as percentages and frequencies, while continuous variables were compared using repeated measure ANOVA. The quality of the surgical field was classified based on Boezaart score (1–2 for clean, and 3–5 for bloody field), and results were reported with risk ratio and risk difference at a 95% confidence interval. Results were expressed as Mean plus minus Standard Deviation (Mean ± SD). Statistical significance was considered at p value < 0.05.

3. Results

Of 141 candidates for rhinoplasty, 11 patients were not eligible, 7 patients were excluded and 3 patients refused to be as a participant. Then, 120 patients were included to be studied as our studied population (Fig. 1, and Table 1).

Of 120 patients were divided into three main groups by block randomization. Based on the parameters collected in Table 1, groups did not show any statistically-significant difference in the baseline characteristics. The blood volume in the end of the operation was

calculated to be 38.3 (±) 12.3 ml in control group, versus 27.7 (±) 12.3 ml in patients receiving low–dose, and 21.7 (±) 12.3 ml in patients receiving high–dose desmopressin group, which demonstrated a statistically-significant difference in blood loss among intervention groups according to ANOVA test ($P < 0.001$, $F = 18.55$). Based on the consequential Bonferroni test, the difference in blood loss volume between patients receiving low–dose of desmopressin and control group was 10.6 ml (CI: 95%: 3.9–17.3), and between control and patients receiving high – dose of desmopressin group was 16.6 ml (CI: 95%: 9.9–23.3), both of them were of statistically-significant difference (both $P < 0.001$) (Table 2).

The duration of operation was not of statistically-significant different between three groups ($p > 0.05$). Evaluation of the effect of study group on systolic blood pressure, diastolic blood pressure, and pulse rate did not show any significance ($P = 0.14$, $P = 0.26$, and $P = 0.09$, respectively). In contrast, the time of surgery had a significant effect on diastolic blood pressure and heart rate according to repeated measure ANOVA ($P < 0.008$, and $P < 0.008$, respectively). No clinically relevant differences were observed among the three groups in hemodynamic parameters.

The quality of the surgical field based on the Boezaart score was classified as clean (0, 1, and 2) and bloody (3, 4, and 5). The control group was considered as a reference and the relative risk of a clean field was assessed (Table 3). Blood and urinary sodium did not change significantly one day after surgery between three groups ($P > 0.05$) (Table 4).

4. Discussion

Bleeding complications pose significant challenges in the realm of open septorhinoplasty, both for the patients and the surgeons. On the patient side, such complications can potentially extend hospital stays, increase healthcare costs, and overall, negatively affect their post-operative satisfaction and recovery trajectory [19,48,53,54]. For surgeons, intraoperative bleeding complications can limit the visibility of the surgical field and extend the duration of the operation, thereby affecting the surgical precision and potentially compromising the quality of the surgical outcome [19,48,55].

This randomized clinical trial scrutinized the effect of varying doses of topical desmopressin on intraoperative bleeding and the surgical field during septorhinoplasty. This outcome could be particularly critical in rhinoplasty, as less blood loss can lead to a reduced soft tissue swelling and bruising, thus allowing for more accurate estimation by the surgeon. In the present study, the use of intranasal desmopressin significantly reduced blood loss during open septorhinoplasty. The findings are consistent with previous studies highlighting the hemostatic benefits of desmopressin [56]. A remarkable aspect was the dose-dependent response observed; a high dose of

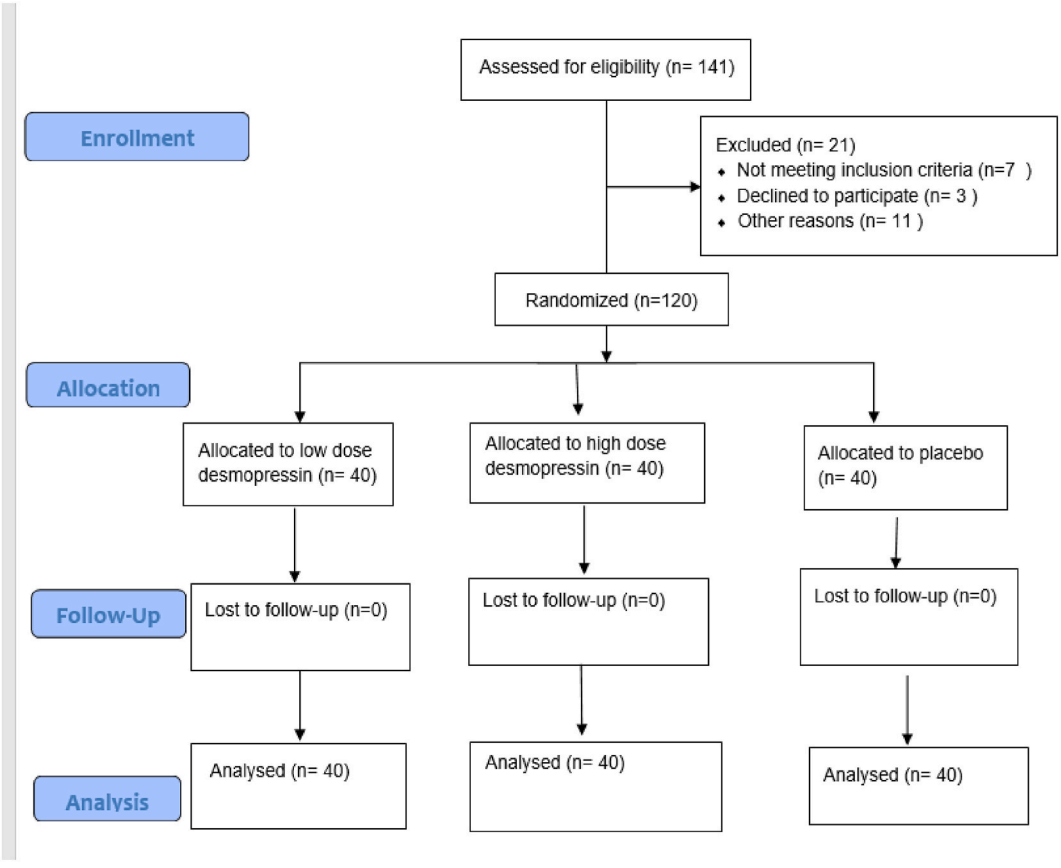

Fig. 1. Patient flow diagram in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Table 1
Demographic and basic features of participants.

	LD-Des *	HD-Des**	Placebo
Female (N, %)	38 (95)	38 (95)	39 (97)
age (year)	28.1 (6.5)	26.9 (6.4)	26.1 (7.4)
Hemoglobin (mg/dl)	12.5 (13)	12.4 (0.9)	12.33 (1.2)
blood sodium	140 (3.1)	139.1 (2.8)	139.8 (3.0)
urine sodium	65.7 (43.1)	73.9 (40.9)	77.3 (45.8)

LD-Des *: low-dose desmopressin.
HD-Des**: high-dose desmopressin.

Table 2
Comparison of intraoperative bleeding between low-dose desmopressin (LD-Des) (ml), high-dose desmopressin (HD-Des) and placebo. [a] Mean (SD). [d] Effect size (95% confidence interval).

Model	LD-Des N = 40	HD-Des N = 40	Placebo N = 40	Mean Difference[a]	p value
Crude	27.65 (12.3)	21.65 (12.3)	38.28 (12.3)		0.000
LD-Des vs. placebo				−10.625 (−17.34, −3.91)	0.001
HD-Des vs. placebo				−16.625 (−23.34, −9.91)	0.000
LD-Des vs. HD-Des				−6 (−12.72, 0.72)	0.096

Table 3
Relative risk of achieving clean surgical field in study groups compared to control group in different times.

Relative risk (RR)	15 min	30 min	45 min	60 min
Low-dose Desmopressin	(072, 1.86) 1.15 P = 0.55	(0.68, 1.73) 1.09 P = 0.72	(0/96,2.70) 1.61 P = 0.07*	(0.62, 1.53) 0.97 P = 0.91
High-dose Desmopressin	(079,1.99) 1.25 P = 0.35	(0.7,1.78) 1.12 P = 0.64	(0.96, 2.70) 1.61 P = 0.07*	(0.67,1.64) 1.50 P = 0.82

Table 4
Urine and serum sodium levels after surgery in participants (mEq/L).

	Blood sodium the day after surgery	Urine sodium the day after surgery
Control group	(16.4)137	(46.7)74.2
Low-dose Desmopressin	(2.9)139.8	(41.7)65.9
High-dose Desmopressin	(2.4)138.7	(40.4)73.2

desmopressin resulted in a more substantial reduction in blood loss compared to a low dose. This outcome aligns with pharmacological principles suggesting that increased doses may elicit more pronounced effects [4,57].

It is noteworthy that the operation duration did not differ significantly among the three groups, which mirrors previous findings indicating that desmopressin's hemostatic effect does not inherently translate into reduced operative times. It might be inferred that the operative time in septorhinoplasty depends on various factors, including individual surgical skills and specific patient characteristics, beyond the scope of desmopressin's influence.

Our study also found that the administration of desmopressin did not result in significant alterations in hemodynamic parameters such as systolic and diastolic blood pressure, and pulse rate. This finding is particularly noteworthy as it suggests a favorable safety profile for desmopressin, aligning with prior reports indicating that desmopressin does not cause significant systemic effects (Jones & Thompson, 2023).

In terms of surgical field quality, our results implied that the use of desmopressin could potentially favor a cleaner surgical field. While these findings are promising, they should be interpreted with caution given the subjective nature of the Boezaart score and the need for further investigation.

Haddady and colleagues assessed the effects of 40 μg (high-dose) desmopressin on 17 candidates for rhinoplasty. They reported a notable decline in upper eyelid ecchymosis, Boezaart score, and intraoperative bleeding in the experimental group when compared to the control. Furthermore, post-operative epistaxis was also observed to be lower in the desmopressin group, although the difference was not statistically significant [41]. These findings are consistent with those of the current study; however, the non-significant disparity could be due to the smaller participant group in this study.

Similar results have been noted in a few studies that examined the effect of desmopressin (both intravenous and topical) in endoscopic sinus surgery. These studies assessed low-dose desmopressin and universally reported a decrease in surgical field blood volume and enhanced Boezaart scores. Unlike previous studies that suggested a decrease in blood volume, the findings of the current study weren't sufficiently convincing to advocate for the use of intranasal desmopressin for securing an optimal surgical field

according to the BOEZAART score. We were unable to identify any significant variance in this parameter across the three study groups. It seems that more accurate results might necessitate larger group sizes. Additionally, the relative risk of achieving a clear surgical field was only marginally significant within the first 45 min of the procedure, underscoring the importance of additional research with more extensive sample sizes.

Consistent with the prior research, our study did not reveal any changes in the blood and urine levels of sodium, even though with the clinical administration of desmopressin. In theory, anti-diuretic functions capable of promoting the fluid retention was of clinical significance. It's been established that side effects such as hyponatremia are more probable with an extended usage and in pediatric cases. One limitation of our research was the employment of a subjective scale for surgical field evaluation. Additionally, future research should aim to exclude the impact of topical vasoconstrictors to reduce confounding variables. A key highlight of our study was the juxtaposition of low and high-dose intranasal desmopressin against a placebo. This comparison demonstrated the effectiveness of both low and high-dose desmopressin as premedication in decreasing blood volume compared to the placebo, with only minor side effects observed. All patients maintained hemodynamic stability, and there were no reports of hyponatremia.

5. Conclusion

According to the inevitable complications of hemorrhage during an open septorhinoplasty surgery, and their detrimental effects on the quality of the surgical field, it seems that conventional approaches are not of enough clinical efficacy, and there is an imperative need for the clinical usage of the more efficient pharmacological interventions with a more prolonged half-life. Based on the results of the present study, our study substantiates the potential benefits of topical (intranasal) administration of desmopressin in an open septorhinoplasty, primarily via it's positive influence on reducing the blood loss in the surgical field. Our findings, combined with the overall safety profile, advocate for the consideration of desmopressin as a valid option in the armamentarium for managing the bleeding rate during a septorhinoplasty. To generalize the results to other surgeries, further investigations, as well as a collaboration among surgeons and pharmacologists are highly recommended.

Author contribution statement

Maliheh Akbarpour: Conceived and designed the experiments; Performed the experiments.
Mir mohammad Jalali: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Maryam Akbari; Fatemeh Azad: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Sevil Nasirmohtaram: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Soudabeh Haddadi: Performed the experiments.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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