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Dexamethasone and ketorolac compare with ketorolac alone in acute renal colic: A randomized clinical trial

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ABSTRACT

Background: Multidrug pain control can be beneficial in relieving pain and limiting narcotic use in renal colic. The purpose of this study was to evaluate the effects of adding dexamethasone to ketorolac on pain control in acute renal colic.

Methods: One hundred twenty patients with renal colic were randomized into comparison and intervention groups to investigate the effect of 8 mg of dexamethasone with 30 mg ketorolac administered immediately after the patient's admission. The primary outcome was pain intensity based on the visual analog scale (VAS), which was assessed at the baseline and after 30 and 60 min of drugs treatment. Also, grade of vomiting and narcotic or antiemetic requirement were measured at the baseline and after the 60-min intervention.

Results: A total of 120 patients were included in the final analysis, with 60 patients (50%) randomized to the comparison group (just ketorolac) and 60 (50%) randomized to the intervention group (ketorolac + dexamethasone). There were no significant demographic differences between groups ($P > 0.05$ for all). Differences in VAS scores were significantly lower in the intervention group after 30 min of drug administration ($P = 0.009$, compared with the control). However, there was not a significant difference in the median VAS score between groups at the baseline and end of the study ($P > 0.05$). At the end of the study, the percent of patients who need to narcotics (35% vs. 58%, $P = 0.01$) and/or antiemetic (12% vs. 28%, $P = 0.022$) were significantly lower in the intervention group compared with the controls.

Conclusions: In comparison with the patients who just received ketorolac, adding dexamethasone provided improved pain control after 30 min of therapy. Furthermore, it decreased opioid requirements and decreased an antiemetic need at the end of the study. Dexamethasone should be considered an important multimodal adjunct for controlling pain and nausea in renal colic.

1. Introduction

Flank pain due to renal colic usually starts with a sudden, severe, and sharp colic in the flanks that radiates toward the lower abdomen, groin, or genitals. Common urinary symptoms are hematuria, dysuria, frequency, and urgency with low voided volumes [1,2]. Pain-induced nausea and vomiting are seen too [1-3]. Differential diagnosis still exists for instance pyelonephritis, other sources of intrinsic or extrinsic ureteric obstruction [2], aortic aneurysm, diverticulitis, appendicitis, and ovarian disorders such as torsion or rupture or miscarriage [4].

Stretching in the renal pelvis leads to stimulation, synthesis and local release of prostaglandins, arachidonic acid metabolites, which stimulate diuresis and vasodilation and thereafter, increase internal pressure. The direct effect of prostaglandins on the ureter leads to smooth muscle spasms in the urinary tract wall [5].

The National Institute for Health and Care Excellence (2019) recommends the use of NSAIDs by any route as the first line of therapy in adults, children, and young people with suspected renal colic. It suggests the use of intravenous paracetamol when NSAIDs are contraindicated or single therapy with NSAIDs did not relive renal colic. Opioids are limited to those for whom both NSAIDs and intravenous paracetamol are contraindicated or are not giving sufficient pain relief. It does not offer antispasmodic drugs for the relief of renal colic [6]. The European Association of Urology guidelines in treating renal colic

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recommend the use of NSAIDs as the first line in all except those with a specific contraindication and suggest NSAIDs are superior to opioids [7].

Narcotics such as codeine and meperidine, and especially morphine are effective in renal colic. The advantages of using these compounds include low price, effectiveness, and convenient titration, but their side effects limit their use. The most important side effects of narcotics include nausea, vomiting, sedation, dizziness, lightheadedness, dependency (risk of addiction), respiratory depression, disorientation, and hypotension [1]. Among them, pethidine is associated with the highest rate of vomiting [7].

Arachidonic acid metabolites that play a major role in the pathology of inflammatory pain [8] are released by the kidney capsule in urolithiasis/calculus-induced obstruction [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) by inhibiting cyclooxygenase (COX) isoenzymes stop the production of these metabolites and relieve inflammatory pain with no suppressive effects on the respiratory system and consciousness level, unlike opioids [2]. Furthermore, in comparison with opioids, while NSAIDs have equivalent effects in the relief of renal colic, they induce less adverse effects and lower the need for rescue analgesia. In this regard, NSAIDs seem preferred analgesic choice in renal colic [9].

Glucocorticoids, a sub-class of corticosteroids often known as steroids and anti-inflammatory medicines, are prescribed for a wide range of conditions; besides anti-inflammatory effects, they have immunosuppressive, anti-proliferative, and vasoconstrictive effects. These drugs act by binding to the intracellular glucocorticoid receptors, which are then transported into the cell nucleus and alter gene transcription to upregulate the transcription of anti-inflammatory genes and/or downregulate the transcription of inflammatory genes. These alterations affect the downstream production of some pro-inflammatory cytokines and chemokine proteins, cell adhesion molecules, and other key enzymes which are involved in the initiation and/or maintenance of the inflammatory response. Therefore, they increase the synthesis of anti-inflammatory mediators and reduce the production of proinflammatory ones [10-12]. Dexamethasone is a potent long-acting glucocorticoid with the least mineralocorticoid effects and is generally prescribed for its anti-inflammatory, immunosuppressant [12], and antiemetic properties [3].

There are reports of dexamethasone being effective in reducing pain, swelling, edema, trismus, nausea, and vomiting after surgery [13-16]. The analgesic effects of dexamethasone are not very clear. However, these effects may be due to inhibition of the synthesis of cyclooxygenase II, prostaglandin formation, and other pro-inflammatory mediators [3,10]. Currently, it is a well-known adjunct for anaesthesiologists in systemic, epidural, or perineural analgesia since it acts synergistically with local anesthetics to obtain a better quality and duration of analgesia, which decreases the need for alternative analgesics, particularly narcotics [17].

Based on the literature and guidelines, multidrug pain control can be beneficial in relieving pain and limiting narcotic use [6,15,16,18]. Against this background, we hypothesized that co- administration of dexamethasone with ketorolac in comparison with ketorolac alone may alleviate renal colic and pain-induced vomiting more effectively and decrease narcotic requirement.To the best of our knowledge, there is no publication about the effect of dexamethasone treatment in combination with an NSAID on pain and vomiting in renal colic.

2. Material and methods

2.1. Study design

This double-blind, randomized clinical trial was designed to evaluate the efficacy of dexamethasone in the relief of renal colic. Patients who were referred to the emergency department of Imam Ali Hospital, Bojnurd, Iran, due to renal colic from Aug 9, 2019 to Jun 8, 2021, were included. Ethical approval for this study was obtained from the Research Ethics Committee in North Khorasan University of Medical Sciences (IR.NKUMS.REC.1398.047). Furthermore, the protocol of the study was registered at the Iranian Registry of the clinical trial (IRCT20190831044653N1). Written informed consent was obtained from all participating patients or their first-degree family members after receiving an explanation of the study. The sample size was determined through clinical significance. Sample size calculations were based on the primary comparisons of Cohen's standard effect, we considered a 95% confidence interval and 80% power and the Cohen standardized effect value of 0.56 (medium effect size) and pain severity as a primary outcome [19] and reached the sample size of 52 patients for each group. However, given the probability of a 15% drop in samples, at least 60 patients were assigned to each group.

2.2. Participants

Patients with flank pain who were admitted to the emergency department of of Imam Ali hospital, were enrolled if the acute renal colic was diagnosed based on the cell blood count, urinary assay, sonography, or CT-scan by a specialist physician. The enrolled patients must be 18–60 years old, with a renal colic severity > 5 based on the 10-cm visual analog scale (VAS) scores.

Exclusion criteria were included pregnancy (confirmed or possible), analgesic therapy during 6 h before admitted to the emergency unit, near history of hemorrhagic diathesis, addiction or recent methadone use, use of warfarin and other anticoagulants, acute abdomen (peritonitis), axillary temperature > 37.7, and BP ≥ 180/100 mmHg; any contraindication for ketorolac including hypersensitivity to aspirin or other NSAIDs, active or history of peptic ulcer disease, a recent history of gastrointestinal bleeding or perforation or suspected or confirmed cerebrovascular bleeding, advanced hepatic or renal disease, patients at risk for renal failure (CrCl<30 ml/min), hyperkalemia, and uncontrolled severe heart failure; and any contraindications for the use of dexamethasone such as hypersensitivity, systemic fungal infections, and liver failure.

2.3. Randomization, interventions, and follow up

Eligible patients were randomly divided into the intervention and comparison groups according to the permuted block randomization sequence. Patients in the intervention group received ketorolac (SD, 30 mg, IV) with placebo (SD, sterile water for injection, IV), while in the comparison group, patients received ketorolac (SD, 30 mg, IV) with dexamethasone (SD, 8 mg, IV). Allocation assignment was concealed from patients and investigators. The pain was assessed on 10-point VAS scores. Enrolled patients were asked by nursing staff to mark their current pain level on this line. The first pain scores immediately before injections and in sequence, 30 min and 60 min after injections were recorded. Furthermore, vomiting grades based on the patient's complaints including grade 0: no nausea or vomiting, grade 1: suffering from nausea, grade 2: transient vomiting and grade 3: vomiting requiring therapy, were recorder immediately before injections and one hour after were documented. The duration of the study was one hour. If no response was observed after one hour, to prevent the enrolled patient from tolerating more pain, narcotics including morphine or pethidine, and antiemetic drugs for instance ondansetron, would be used and recorded.

Following enrollment in the study, variables including age, sex, body weight, and systolic and diastolic blood pressure were extracted from the medical record.

Patients were monitored in terms of changes in the CBC and urinary assay.

2.4. Outcome measures

The primary outcome was pain severity based on the VAS. Therefore, all eligible patients had been followed from the admission and every 30 min after receiving drugs for one hour. Also, the secondary

outcome in this trial was the grade of vomiting and the need for narcotics or antiemetic drugs at the end of the study. In this regard, all eligible patients had been followed from the admission and one hour after drug therapies.

2.5. Statistical analysis

We used graphical methods and Shapiro-Walk's tests to check the normality of each variable before data analysis. To describe the quantitative variables, statistics presented for variables included counts and percentage for categorical variables, and mean ± (SD) or median (Q1–Q3) for continuous variables. Categorical variables were compared between two groups using Chi-Squared tests or Fisher's exact test. Normally distributed data were analyzed using an independent-sample *t*-test, and the results were presented as mean ± (SD). Non-normally distributed data were analyzed using Mann-Whitney *U* test, and the results were presented as median (Q1–Q3). For evaluating within-group differences in normally and non-normally distributed data paired sample t-test and Wilcoxon signed-rank test were used, respectively. Also, an adjusted comparison of between-group outcomes was done using parametric and non-parametric ANCOVA considering changes in baseline value of outcome as a covariate. The data were analyzed through SPSS version 22.

3. Results

As presented in Fig. 1, a total of 517 patients with renal colic applied to participate in the study. Of these, 120 patients were eligible for our study. Eligible patients were randomly allocated into the intervention and comparison groups according to permuted block randomization.

The median pain severity at the baseline was 9.5 (8–10) for patients with renal colic. The mean age of the patients was 37.62 (±9.03) and 70% of the patients were male. The mean body weight and blood pressure were 74.75 (±11.13) kg and 128.94 (±11.87)/79.74 (±8.97) mmHg, respectively. Most of the patients said, 58% had no nausea or vomiting (grade 0), 32% suffered from nausea (grade 1), 9% had transient vomiting (grade 2), and only 1% had vomiting requiring therapy (grade 3).

Participant characteristics at the baseline are shown in Table 1. The results show that there were no statistically significant differences in respect of basic characteristics across groups at the beginning of the study ($p < 0.05$).

Follow-up of the patients undergoing treatment started at the time of admission and at the time of treatment assignment and continued for one hour. During this period, the median (IQR) of the pain severity was 3.5 (0.25–6) and 1 (0–5) after 30 and 60 min of drug therapy.

As shown in Table 2, the VAS scores decreased significantly within the two groups following 30 and 60 min of intervention (P for within-group comparison <0.001). Also, the VAS score was significantly different between the two groups after 30 min' follow-up (P for between-group comparison = 0.009). However, the pain scores in the intervention group were not significantly different at the baseline and end of the study compared to the comparison group (Table 2).

After adjusting for scores at the baseline using the ANCOVA test, the two groups were significantly different after 30 min' follow-up ($P = 0.005$). However, according to the ANCOVA tests adjusted for baseline measures, there were no significant differences in between two groups in the pain scores at the baseline and end of the study.

According to the results of Table 3, at the end of the study, 58% of the patients in the standard group and 35% in the intervention group required a narcotic to relieve the pain ($P = 0.01$), and 28% in the standard group and 12% in the intervention needed an antiemetic ($P = 0.022$).

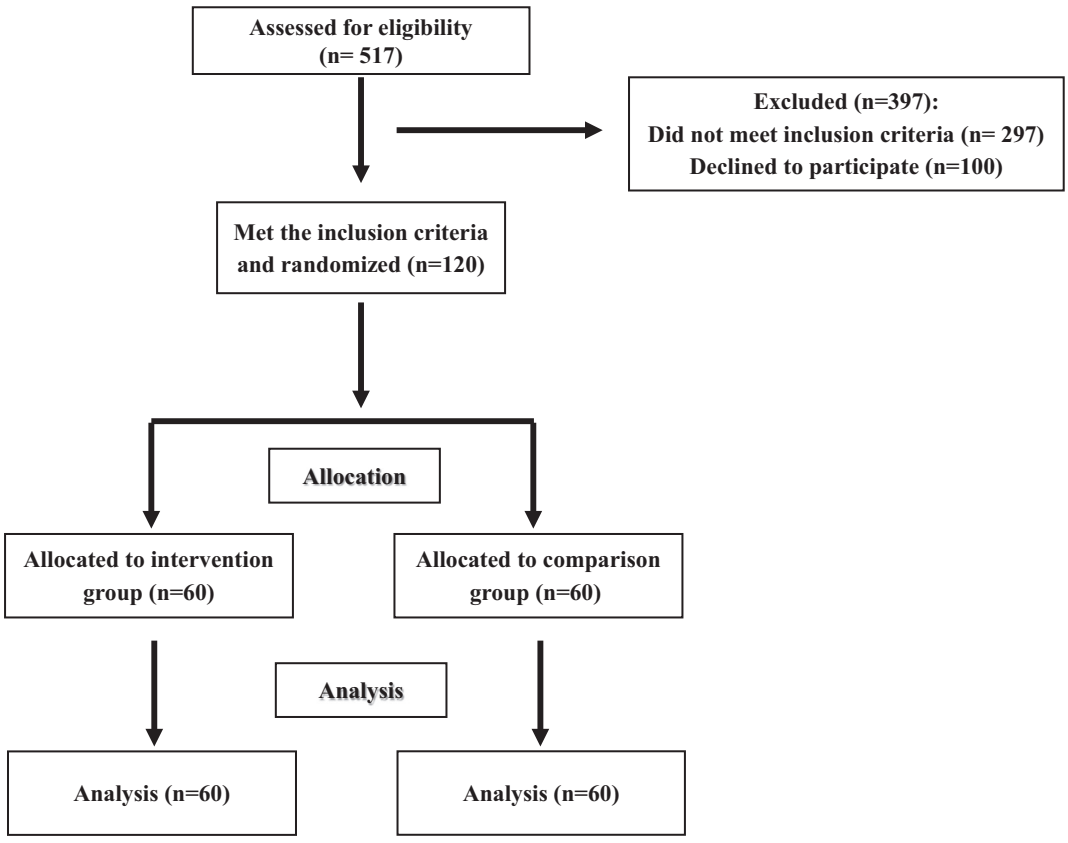

Fig. 1.. Summary of patients' flow diagram.

Table 1
Participant characteristics at baseline.

Variables		Groups		P- value
		Intervention ($N = 60$)	Control ($N = 60$)	
Age, median (IQR), y		35 (30–44)	38 (32–44)	0.2*
Body weight, mean (SD), Kg		75.38 (12.34)	74.06(9.79)	0.61**
Systolic blood pressure, median (IQR), mmHg		130 (120−130)	130 (125–138)	0.27*
Diastolic blood pressure, median (IQR), mmHg		80 (75–85)	80 (75–85)	0.47*
Initial pain score, median (IQR), cm		9.5 (8–10)	9.5 (8–10)	0.77*
Sex (male), No (%)		42 (70)	40 (70)	1***
Vomiting grade****, No (%)	0, No (%)	39 (65)	31 (52)	0.27***
	1, No (%)	15 (25)	23 (38)	
	2, No (%)	6 (10)	6 (10)	

* *P* value for between-group comparison of nonparametric quantitative data using Mann-Whitney *U* test.
** *P* value for between-group comparison of parametric quantitative data using independent-sample *t*-test.
*** *P* value for between-group comparison of qualitative data using Chi-squared test.
**** Grade 0: no nausea or vomiting, grade 1: suffering from nausea, grade 2: suffering from vomiting.

4. Discussion

For patients with renal colic admitted to the emergency unit, giving single intravenous ketorolac (30 mg) or a combination of ketorolac plus dexamethasone (8 mg) significantly decreased the VAS scores after 30 min and 60 min in comparison to the baseline. However, adding dexamethasone resulted in a significant decrease in the VAS scores for pain after 30 min' follow-up compared with the group just received ketorolac. Furthermore, the need for narcotics and antiemetic drugs at the end of the study, 60 min follow up, was significantly less in patients who received the combination of ketorolac plus dexamethasone. To our knowledge, this is the first clinical trial demonstrating the benefits of dexamethasone use in renal colic.

Our findings are consistent with Klag et al. study that emphasized preoperative administration of dexamethasone (10 mg, SD) decreased postoperative VAS scores, and reduced narcotic and antiemetic requirement following total shoulder arthroplasty. In this study, all patients in the control and dexamethasone group received an intraoperative local infiltration cocktail composed of ketorolac (30 mg), ropivacaine (5%, 300 mg), and epinephrine (10 mg). Therefore, the combination of dexamethasone with ketorolac was superior to ketorolac in controlling pain and nausea [18].

Table 2
Pain score comparison in two groups at baseline and after follow-up.

Variable		Groups		P*	Adjusted P
		Intervention ($n = 60$)	Control ($n = 60$)		
Pain score	Baseline	9.5 (8,10)	9.5 (8,10)	0.77	
	30 min	3.5 (0.25,6)	5 (3,7)	0.009	0.005#
	Change	−5 (−7,−2)	−3 (−6,−1)	0.014	
	P**	0.00	0.00		
Pain score	Baseline	9.5 (8,10)	9.5 (8,10)	0.77	
	60 min	1 (0,5)	4 (0,6)	0.07	0.068#
	Change	−7 (−9,−3)	−5 (−9,−2)	0.21	
	P**	0.00	0.00		
Pain score	30 min	3.5 (0.25,6)	5 (3,7)	0.009	
	60 min	1 (0,5)	4 (0,6)	0.07	0.68&
	Change	−1 (−3,0)	−2 (−3,0)	0.15	
	P**	0.00	0.00		

Nonparametric quantitative data reported as median (Q1, Q3). P value considered significant if <0.017.
* *P* value for between-group comparison of nonparametric quantitative data using Mann-Whitney *U* test.
** *P* value for within-group comparison of nonparametric quantitative data using Wilcoxon signed-rank test.
\# *P* value using nonparametric ANCOVA test adjusted for baseline measure.
\& *P* value using nonparametric ANCOVA test adjusted for measure at 30 min after intervention.

In contrast with our study in which the combination of dexamethasone plus ketorolac is compared with ketorolac, Momesso et al. study compared the combination of dexamethasone plus ketorolac with dexamethasone. In agreement with our study, Momesso et al. research showed a combination of dexamethasone and ketorolac should be considered for preemptive acute postsurgical pain management in third molar surgery. Both show superior benefits of combination therapy of a glucocorticoid plus an NSAID in controlling pain [20].

Another study reported 0.5 mg/kg intravenous administration of dexamethasone after induction and before the commencement of the operation decreases VAS values on post-operative tonsillectomy pain. This observation is in agreement with the result of our study that shows adding dexamethasone has superior effects in control of pain [14].

Furthermore, the results from a meta-analysis on the efficacy and safety of dexamethasone for pain management after total-knee arthroplasty verify our data that reported administering dexamethasone could significantly reduce postoperative pain scores at 12, 24, and 48 h and opioid consumption at 12 h after total-knee arthroplasty surgery. The results indicated that dexamethasone was associated with a significant reduction in the incidence rate of postoperative adverse effects including nausea, vomiting, and pruritus [15].

A prospective, randomized, double-blind, placebo-controlled study has shown a single preoperative dose of dexamethasone (8 mg, IV) delays patient request for analgesia, decreases postoperative nausea and vomiting, and reduces total narcotic consumption in patients undergoing total laparoscopic hysterectomy [16].

It has been shown that dexamethasone (8 mg, SD, Orally) is more effective than ketorolac (20 mg, SD, sublingual) in controlling pain, swelling, and trismus following mandibular third molar removal [21]. This might be related to the suppression of multiple signaling pathways involved in the inflammatory response for instance promotion in lipocortin and vasocortin activity, the former inhibits PLA2 and the latter inhibits histamine release, in addition to repression COX and the synthesis of eicosanoids [22-24]. Based on the Dionne et al. study, this might be related to the dexamethasone dose. In contrary to Martins-de-Barros et al., Dionne et al. showed although dexamethasone at a dose of 4 mg orally at 12 h and 4 mg intravenously one hour before the third molar surgery decreased both PGE2 and TxB2 level at the site of injury, it had no superior analgesic effects in comparison to ketorolac. It seems dexamethasone in this does dose not suppress PGE2 level sufficiently to diminish peripheral sensitization of nociceptors post tissue injury [17].

The body responds to pain via the sympathetic nervous system, neuroendocrine system, and immune system. The sympathetic nervous system is the “fight or flight” system that increases the performance of respiratory and cardiovascular systems and reduces gastro intestinal function. Therefore, pain-induced sympathetic nervous system activation leads to a reduction in food digestion that can

Table 3
Clinical characteristics of the study groups.

Variables		Groups		P- value*
		Intervention No (%) (n = 60)	Control No (%) (n = 60)	
Need for narcotics 60 min after therapy		21 (35)	35 (58)	0.01
Need for antiemetic 60 min after therapy		7 (12)	17 (28)	0.02
Vomiting grade**	0, NO (%)	50 (83)	47 (78)	0.24
	1, NO (%)	9 (15)	8 (13)	
	2, NO (%)	1 (2)	5 (9)	

* *P* value for between-group comparison of qualitative data using Chi-squared test.
** Grade 0: no nausea or vomiting, grade 1: suffering from nausea, grade 2: suffering from vomiting.

result in nausea and vomiting [3,25]. In response to pain and in relation to the sympathomedullary pathway and hypothalamic-pituitary-adrenocortical (HPA) axis, cortisol, adrenaline, and noradrenaline are released [26,27]. Furthermore, tissue damages activate the immune system and orchestrate inflammatory responses that stimulate sensory nerve ending and provoke pain. This causes transmitting the pain signal to the dorsal horn, and also triggering the inflammation at the site of injury [28,29]. PGE2 is detectable in the first postoperative samples and increases coincident with the onset of postoperative pain [17]. As mentioned in previous parts, many studies have emphasized the effectiveness of corticosteroids in controlling postoperative nausea, vomiting, opioid consumption [15,16], and of course inflammatory pain [14-16,18,21] in which the release of inflammatory mediators sensitize the peripheral nociceptors that causes hyperalgesia [30], and pain-induced nausea and vomiting [3,18,25].

5. Limitations

The present study also has some limitations that could be used to improve future research. Our study did not consider any cut-off point in the need for narcotics or antiemetic drugs. It is not clear whether this requirement is related to the real need of the patients or is based on research bias. Furthermore, evaluating the expression of local prostanoids, arachidonic acid metabolites, including PGE2 (a product of both COX-1 and COX-2) and TxB2 (a product of COX-1) 30 min and 60 min after therapies could explain the molecular mechanism of drugs. It could clarify any relation between antianalgesic effects of tested drugs and prostanoids' level in a time-dependent manner, the data that was missed herein.

6. Conclusions

This study showed benefits exist with the combination of ketorolac plus dexamethasone in decreasing renal colic. Furthermore, it decreased narcotics requirement or antiemetic use at the end of the study. Based on the results, the combination of ketorolac and dexamethasone might provide patients with some benefits and should be considered as a viable option in acute renal colic.

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Author contributions

AR, MR, and HS conceived the study and designed the study. AR, EF, PL, S·S H, and RH supervised the conduct of the study and data collection. HS analyzed the data. MR and HS drafted the manuscript and all authors contributed substantially to its revision. MR and AR takes responsibility for the paper as a whole.

Credit authorship contribution statement

Abdolah Razi: Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Esmaeil Farrokhi:** Writing – review & editing, Supervision, Data curation. **Pegah Lotfabadi:** Writing – review & editing, Supervision, Data curation. **Somayeh Sadat Hosseini:** Writing – review & editing, Supervision, Data curation. **Hasan Saadati:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis. **Ramin Haghighi:** Writing – review & editing, Supervision, Data curation. **Maryam Rameshrad:** Writing – original draft, Methodology, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest in regard to this research or its funding.

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