Safety and efficacy of ketamine-dexmedetomidine combination versus dexmedetomidine alone in cirrhotic patients undergoing upper gastrointestinal endoscopy: a prospective controlled clinical trial

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Abstract

Background: Patients with liver cirrhosis commonly undergo diagnostic and/or therapeutic upper gastrointestinal endoscopy (UGIE). These fragile patients are at increased risk to develop complications as most sedative drugs are metabolized by the liver.

This prospective, randomized controlled trial was performed to compare sedo-analgesia with ketamine-dexmedetomidine combination (KD1) (n = 35) versus dexmedetomidine alone (D2) (n = 35) in cirrhotic patients undergoing UGIE.

Results: UGIE could be performed effectively and safely with the KD1 (n = 35) group compared with the D2 group as no significant change in hemodynamics (HR and MBP) and O2 saturation (SPO2) from baseline values (P value > 0.05) while the D2 group revealed a statistically significant drop in hemodynamic parameters when compared with the KD1 group (P value < 0.001).

Also, the induction time was statistically significantly lower in the KD1 group (3.9 ± 0.9 min) compared to the D2 group (5.2 ± 1.1 min) (P value < 0.05).

Recovery time was statistically significant faster in the KD1 group (4.5 ± 1 min) versus the D2 group (6.1 ± 1.6 min) with P value < 0.05.

Endoscopic procedure was highly effective in KD1 (100%) compared with D2 (71.4%) with P value < 0.001.

Supplementary fentanyl was given to 10 patients (28.6%) in the D2 group versus 0% in the KD1 group (P value < 0.001).

Regarding post-operative adverse effects, there was statistically significant discomfort in D2 (28.6%) compared with KD1 (5.7%) with P value = 0.02. Also, gagging was statistically significant in D2 (22.9%) compared with KD1 (2.9%) with P value = 0.03.

Conclusions: The ketamine-dexmedetomidine sedo-analgesia group is highly effective than the dexmedetomidine-alone group in UGIE procedures with rapid induction time, good hemodynamic stability good recovery profile with less post-operative adverse effects.
Background
Upper gastrointestinal endoscopy (UGIE) is a common maneuver used for patients with liver cirrhosis for diagnostic and/or therapeutic interventions either for banding or injection sclerotherapy (Cheung et al., 2001). These endoscopic maneuvers require conscious sedation and analgesia to perform examination safely (Habib & Sanyal, 2007). However, patients with liver cirrhosis are at increased risk to develop complications which are related to sedation as most sedative drugs are metabolized by the liver (Verbeeck, 2010). The available known sedatives such as benzodiazepines, opioids, and even propofol can cause respiratory depression and delayed recovery in these fragile patients (Bamji et al., 2010).

Dexmedetomidine is a highly selective alpha 2-adrenoceptor agonist which is used for sedation of mechanically ventilated patients in the intensive care unit (ICU) and in non-intubated adult patients before and/or during surgical and other procedures without depressing respiratory function (Hoy & Keating, 2011). Unlike patients sedated with propofol, patients sedated with dexmedetomidine are easily arousable without exhibiting irritation (Abdelmalak et al., 2007). However, there are increasing number of reports regarding combination of dexmedetomidine with ketamine (Jalowiecki & Rudner, 2005; Mester & Esley, 2008). When used together, ketamine may prevent bradycardia and hypotension induced by dexmedetomidine whereas dexmedetomidine may prevent tachycardia, hypertension, salivation, and emergence phenomenon from ketamine. Also, the use of ketamine to initiate sedation speeds the onset of sedation thus eliminating the slow onset time when using dexmedetomidine as the sole agent (Mahmoud & Tyler, 2008).

So, this study was performed to evaluate the efficacy and safety of sedative (UGIE) with ketamine-dexmedetomidine combination versus dexmedetomidine alone in patients with liver cirrhosis.

Methods
This prospective, randomized, controlled, double-blind clinical study was carried out in the endoscopy unit of tropical medicine department in collaboration with the anesthesia department of Qena University Hospitals in the time period from January 2017 to July 2018 over 70 adult patients aged 18–60 years with compensated liver cirrhosis, child-Pugh score A or B, referred for diagnostic and/or therapeutic UGIE after obtaining ethical committee approval from Qena University Hospitals institutional review board at 5 December 2016.

Exclusion criteria were age less than 18 or more than 60 years, child-Pugh score C, need for emergency endoscopy, hemodynamically unstable patients, significant cardiopulmonary disease, hepatic encephalopathy, renal disease, neurologic diseases such as Parkinson’s disease and Alzheimer’s disease, use of sedatives or narcotics one week prior to the endoscopy time, anticipated airway difficulties, and allergy to the used drugs.

After obtaining written informed consent, patients were randomized into two equal groups using a computer-generated sequence of random numbers and a sealed envelope technique. Study drugs were prepared by an anesthesiologist who did not participate in the procedure; this study was conducted in a double-blind manner as neither the administrator of the drug nor the patient know the nature of drug given as follows:

- Group I (KD): (n = 35) thirty-five patients who received intravenous (I.V.) ketamine in a dose of 1 mg/kg diluted in 5 ml normal saline followed by infusion of dexmedetomidine (Precedex, 100 μg/ml, Hospira, USA) in a rate of 0.2–0.6 μg/kg/hour until the Ramsay Sedation Scale increased to 4–5 and bispectral range of 50–70 was adjusted. Supplementary fentanyl 25 μg was administered intravenously as rescue sedo-analgesic when required and recorded.
- Group II (D): (n = 35) thirty-five patients who received (I.V.) dexmedetomidine in a dose of 0.5 μg/kg diluted in 5-ml normal saline followed by continuous infusion of dexmedetomidine in a rate of 0.2–0.6 μg/kg/hour (Precedex, 100μg/ml, Hospira, USA) until Ramsay Sedation Scale increased to 4–5 and bispectral range of 50–70 was adjusted. Supplementary fentanyl 25 μg was administered intravenously as rescue sedo-analgesic when required and recorded.

All patients were subjected to thorough history taking physical examination laboratory investigations (complete blood count, liver function tests, coagulation profile, renal function tests, random blood sugar), abdominal U.S., and electrocardiography (E.C.G.) before the endoscopy procedure.
The diagnosis of liver cirrhosis was based on available history, serological testing, radiologic imaging and liver histology. Staging of cirrhosis was determined by Child-Pugh classification.

Upon arrival to the endoscopy unit, monitoring of E.C.G, heart rate (HR), non-invasive arterial pressure measurement (NIBP), pulse oximetry (SPO₂) was started using Datex-ohmeda (GE Healthcare Co., USA) and continued till shifting out to the recovery room. The baseline values of H.R., mean arterial pressure (MAP), SPO₂, and respiratory rate (RR) were recorded. Topical pharyngeal anesthesia was administered by spraying metered dose of 10% lignocaine.

Following 8 hours period of fasting before the procedure, peripheral I.V. line established with a 20G cannula and lactated Ringer’s was infused at a rate of 6–8ml/kg/hour and oxygen 3 l/min was administered through a nasal cannula. During the procedure, monitoring of HR, MAP, SPO₂, and RR was continued every 2 min for the first 10 min, thereafter every 5 min until the end of the procedure.

The endoscope was introduced when the patient achieved the desired level of sedation of 4–5 according to the Ramsay Sedation Scale (RSS) (Sessler et al., 2008). If awake, Ramsay1—anxious, agitated, or restless; Ramsay 2—cooperative, oriented, and tranquil; Ramsay 3—responds to commands only. If asleep, Ramsay 4—brisk response to light glabellar tap or light auditory stimulus; Ramsay 5—sluggish response to light glabellar tap or light auditory stimulus; Ramsay 6—no response to light glabellar tap or light auditory stimulus. The BIS electrode was placed on the forehead of each patient and the BIS index range of 50–70 was adjusted by titrating the dexmedetomidine infusion rate. Sedation levels were checked every 2–3 min by a light glabellar tap or loud noise.

Induction time (time from starting the study drug(s) until achieving the target of RSS = 4–5 and BIS = 50–70). Procedure time (time from insertion to removal of the endoscope) and recovery time (time from stoppage of drug infusion to achieving RSS = 1, BIS = 90, and modified Aldrete score 10/10 (Aldrete, 1995) were recorded for each patient in the study groups. Occurrence of adverse effects like hypotension, hypertension. Desaturation, apnea, gagging, and retching was also recorded during the procedure. All endoscopies were carried out by single endoscopist.

The patients’ satisfaction regarding discomfort (pain and gagging) during the procedure was assessed using the visual analogue score (VAS) in the recovery room to assess efficacy of sedation. All patients were asked to place a vertical mark on a 10-cm straight line to represent procedural pain, (0 = no pain, 10 = worst pain imaginable). Endoscopist satisfaction regarding retching and difficulty during the procedure was assessed using VAS (0 = no retching/difficulty, to 10 = maximum retching/difficulty).

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin were followed up 3 days after the endoscopic procedure to evaluate hepatic function after the use of dexmedetomidine.

Efficacy: The proportion of complete procedures performed by using the initial proposed sedation scheme. The sedation scheme was considered ineffective when the procedure was interrupted by agitation or intolerance by the patient despite the maximum sedative dose.

Safety: frequencies of the following complications during procedure or recovery time:

1. Hypoxemia.
2. Hypotension.
3. Bradycardia.

Hypoxemia was defined as SPO₂ < 90% recorded by pulse oximetry and managed by increasing oxygen flow non-invasively to 6–10 l/min and chin-lift or jaw thrust maneuver.

Hypotension was considered as 20% reduction in MAP compared with basal value and was treated with bolus dose of ephedrine 5–10 mg I.V. and 250 ml. of lactated Ringer’s solution. Also, bradycardia was considered as 20% reduction in HR compared with the basal value and was treated with atropine I.V. 0.01mg/kg.

A: The primary outcomes were the time taken for adequate sedation (induction time) and efficacy (the proportion of complete procedures performed by using the initial proposed sedation scheme), while secondary outcomes were hemodynamic stability incidence of adverse effects and liver function tests.

**Sample size**

Sample size calculation was done using online power/sample size calculator (http://www.stat.ubc.ca). The means of time taken after adequate sedation (RSS = 4–5) with either ketamine-dexmedetomidine or dexmedetomidine alone was considered the primary end point of this study. We hypothesized that detectable difference between the means of time taken for adequate sedation after treatment with either of both regimens = 2 min. If we estimated a S.D. for this prospective power analysis as 20% and an α value of 0.05, the power of study would be 80%. Sample size calculated to be 27 patients per group. To reduce the possibility of dropouts, we enrolled 35 patients per group.

**Statistical analysis**

Statistical analysis was performed using the statistical package version 21 (SPSS Inc., Chicago, IL, USA). Numerical data were presented as mean ± S.D. and categorical data as number and/or percentage (%). The unpaired t-test was used for comparison of the means of
all variables between the two groups. Whereas changes in data within the same group (HR, MAP, RR, and SPO$_2$) were analyzed using repeated measures analysis of variance.

Paired $t$-test or Wilcoxon’s signed rank test was used to compare the pre- and post-procedural AST, ALT, and total bilirubin in both groups.

Sex ratio and incidence of side effects were analyzed with chi-square test or Fisher's exact test as appropriate. A $P$ value of less than 0.05 was considered statistically significant.

**Results**

Seventy six patients screened for inclusion in the present study and only seventy patients were enrolled in this randomized controlled trial (Fig. 1). The two groups were comparable as regard to age, sex, weight, height, ASA physical status (II or III), child-Pugh score, basal hemodynamic parameters, and oxygen saturation (Table 1).

Regarding hemodynamic changes, the heart rate (HR) and mean arterial pressure (MAP) were statistically significant lower in group II (D$_2$) when compared to group I (KD$_1$) during the procedure ($P < 0.001$) (Figs. 2 and 3).
Also, group I (KD₁) showed no statistically significant differences in hemodynamic parameters (HR, MAP) during the procedure and early recovery when compared with baseline values (P value > 0.05), while group II (D₂) revealed statistically significant drop in hemodynamic parameters (HR, MAP) during the procedure and early recovery when compared with their baseline values (P value < 0.05).

The induction time was statistically significantly lower in group I (KD₁) (3.9 ± 0.9 min) compared to group II (D₂) (5.2 ± 1.1 min) (P value < 0.001). There were no statistically significant differences between the two groups as regard to procedure time (P value = 0.15). Recovery time was statistically significant lower in group I (KD₁) compared to group II (D₂) (4.5 ± 1 min versus 6.1 ± 1.6 min respectively) (P value < 0.001) (Table 2).

The endoscopic procedure was highly effective in group I (KD₁) (100%) (35 patients) compared with group II (D₂) (71.4%) (25 patients) with statistically significance difference (P value < 0.001), with statistically significant endoscopist satisfaction (100%) (35 patients) versus 71.4% (25 patients) (P value < 0.001). Patient comfort (100%) (35 patients) in group KD₁ versus 82.9% (29 patients in group D₂) with statistically significant difference (P value = 0.02). Also, supplementary fentanyl was given to 10 patients (28.6%) in group II (D₂) for experiencing movement, pain, or grimaces during the procedure compared to 0% in group KD₁ (P value < 0.001) (Table 3).

Regarding post-operative adverse effects, there were statistically significant discomfort and gagging in group II (D₂) compared with group I (KD₁) (28.6% (10

Table 1  Demographic data and baseline hemodynamic parameters in the two studied groups

| Parameter                        | KD₁ (n = 35) | D₂ (n = 35) | P value |
|----------------------------------|-------------|-------------|---------|
| Age (years), mean ± SD           | 54.9 ± 5.6  | 55.7 ± 6.1  | 0.57 (NS) |
| Sex (male:female)                | 26:9        | 27:8        | 1 (NS)  |
| Weight (kg), mean ± SD           | 74.6 ± 4.5  | 76.3±5.1    | 0.14 (NS) |
| Height (cm), mean ± SD           | 176.9± 5.3  | 178.7±5.1   | 0.15 (NS) |
| ASA grade (II:III)               | 26:9        | 27:8        | 1 (NS)  |
| Child-Pugh score (A:B)           | 25:10       | 26:9        | 1 (NS)  |
| HR (beats/min), mean ± SD        | 88.4±21.1   | 89.6±18.3   | 0.8 (NS) |
| Mean arterial pressure (mmHg), mean ± SD | 88.1±6.2 | 90.1±5.2 | 0.15 (NS) |
| Oxygen saturation (SpO₂), mean ± SD | 98.5±0.7 | 98.8±0.6 | 0.06 (NS) |

KD₁, ketamine-dexmedetomidine group, D₂, dexmedetomidine group.
ASA American Society of Anesthesiologists, HR heart rate.
Significant; NS non-significant.

Fig. 2 Heart rate changes in the studied two groups. KD₁, ketamine-dexmedetomidine group. D₂, dexmedetomidine group. HR, heart rate. Statistically significant drop of HR in group D₂ compared with group KD₁ (P value < 0.001).
patients) versus 5.7% (2 patients) and (22.9% (8 patients) versus 2.9% (1 patient) respectively with \(P\) value = 0.02 and 0.03 respectively. There were no statistically significant difference in salivation between the two studied groups \((P\) value = 0.61) (Table 4).

There were no statistically significant differences between the two studied groups regarding liver function tests (AST, ALT, and bilirubin) before and 3 days after the procedure (Table 5).

**Discussion**

The ideal pharmaceutical drugs for conscious sedation during upper gastrointestinal endoscopy are still being searched for especially in hepatic patients. Care must be taken to balance patient comfort, hemodynamic stability, post-procedure adverse effects, and the possibility of deterioration of liver function parameters (Tolia et al., 2000).

The aim of the present study was to compare the efficacy and safety of dexmedetomidine alone with ketamine-dexmedetomidine combination as a sedo-analgesic in hepatic patients undergoing UGIE.

The present study revealed that ketamine-dexmedetomidine combination is more effective (as the rate of desired sedation achieved was higher) and safer (as it is associated with least hemodynamic fluctuations and least post-operative adverse effects) than the dexmedetomidine group while the studied two groups were safe regarding liver function parameters.

Also, the ketamine-dexmedetomidine group was associated with a higher level of patient and endoscopist satisfaction together with faster recovery.

Upper gastrointestinal endoscopies are stressful, frequently performed non-invasive procedures used for diagnosis or management (Waring et al., 2003). The primary goals for sedation during UGIE are maintenance of spontaneous respiration while secondary goals include amnesia, anxiolysis, and analgesia (Tolia et al., 2000).

Ketodex is a combination of ketamine and dexmedetomidine that balances the sympato-inhibitory effects of dexmedetomidine with the cardio-stimulatory effects of ketamine provides adequate sedation and analgesia and maintains spontaneous respiration (Levanen et al., 1995).

**Table 2** Comparison of induction, procedure, and recovery times in the two studied groups

| Parameters                     | KD\(_1\) (n = 35) | D\(_2\) (n = 35) | \(P\) value |
|-------------------------------|-------------------|-----------------|-------------|
| Induction time (min), mean ± SD | 3.9 ± 0.9*        | 5.2 ± 1.1       | < 0.001     |
| Procedure duration (min), mean ± SD | 6.1 ± 0.8        | 6.4 ± 0.9       | 0.15 (NS)   |
| Time to recovery (min), mean ± SD | 4.5 ± 1*         | 6.1 ± 1.6       | < 0.001     |

\(KD\(_1\)\), ketamine-dexmedetomidine group, \(D\(_2\)\), dexmedetomidine group

*Significant; \(NS\) non-significant

**Table 3** Efficacy, endoscopist satisfaction, patient comfort, and supplementary fentanyl in the two studied groups

| Parameter                      | KD\(_1\) (n = 35) | D\(_2\) (n = 35) | \(P\) value |
|-------------------------------|-------------------|-----------------|-------------|
| Efficacy, n (%)               | 35 (100)*         | 25 (71.4)       | <0.001      |
| Endoscopist Satisfaction, n (%) | 35 (100)*         | 25 (71.4)       | <0.001      |
| Patient Comfort, n (%)        | 35 (100)*         | 29 (82.9)       | 0.02        |
| Supplementary Fentanyl, n (%) | 0 (0)*            | 10 (28.6)       | <0.001      |

\(KD\(_1\)\), ketamine-dexmedetomidine group, \(D\(_2\)\), dexmedetomidine group

*Significant; \(NS\) non-significant
The present study revealed that the ketamine-dexmedetomidine group showed no significant differences in hemodynamic parameters from the baseline, adequate level of sedation, and no respiratory depression and endoscopy could be performed with ease in all the cases without any interruption.

These results are in accordance with Bali & Patel (2017) who concluded that a combination of dexmedetomidine and ketamine in the UGIE procedure is clinically effective and safe with a good recovery profile.

Although dexmedetomidine has been reported to be effective in non-invasive procedures, it has not been universally effective when used as a sole agent for invasive procedures including gastrointestinal endoscopy (GIE).

Early experience with this medication revealed it to be ineffective in UGIE in the pediatric population (Tobias & Berkenbosch, 2002). Also, a prospective randomized trial in adults comparing dexmedetomidine with fentanyl or meperidine-midazolam for sedation during colonoscopy, concluded that dexmedetomidine resulted in a less effective sedation, a higher incidence of adverse events, and a delay in the time to discharge (Jaloweicki et al., 2005). These studies were in accordance with the present study regarding the hemodynamic derangement that occurred with the dexmedetomidine group as it recorded significant bradycardia and a decrease in the blood pressure to a significant level compared with the basal values and the requirement of another analgesic agent for completion of the procedure. However, conflicting results demonstrating the efficacy of dexmedetomidine alone has been reported by other investigators, Dere et al. reported that dexmedetomidine at a loading dose of 1 μg/kg followed by an infusion of 0.5 μg/kg/hour was superior to midazolam (0.05 mg/kg) and fentanyl (1 μg/kg) during colonoscopy in 60 adult patients (Dere et al., 2010).

Demiraran et al. demonstrated that dexmedetomidine (loading dose of 1 μg/kg followed by an infusion of 0.2 μg/kg/hour was more effective than midazolam (0.07 mg to a maximum of 5 mg) during UGIE in adults (Demiraran et al., 2007).

The conflicting results observed in the various studies regarding the efficacy of dexmedetomidine may be explained by the different doses used and the patient population studied.

Giving our expectations with increasing the dexmedetomidine dose when used alone and its hazardous effects on the heart rate and myocardial function especially in hepatic cirrhosis patients, we preferred the combination of dexmedetomidine and ketamine to provide an optimal level of sedation and analgesia with limited effects on respiratory and cardiovascular functions. The use of ketamine provides several benefits including the provision of analgesia which is not present with dexmedetomidine increase in HR and BP to offset the bradycardia of dexmedetomidine and a more rapid onset when compared to dexmedetomidine alone. Also, dexmedetomidine has been reported to prevent several adverse effects of ketamine including emergence agitation, excessive salivation, and stimulation of the cardio-vascular system (Levanen et al., 1995).

In a study conducted by Bali and Patel, they gave dexmedetomidine (1.5 μg/kg) I.V. bolus slowly over 5 min followed by ketamine (0.5 mg/kg) before starting the endoscopic procedure in 60 patients of ASA I, II, and III aged 18–60 years, scheduled for UGIE. There were no significant hemodynamic changes from the baseline none of the patients had bradycardia, hypotension, or desaturation and there was no need for any active airway intervention (Bali & Patel, 2017).

Tobias presented a descriptive study of several reports about the use of a combination of ketamine and dexmedetomidine for procedural sedation (Tobias, 2012) and revealed that ketamine could prevent the decrease in blood pressure and heart rate which had been observed with dexmedetomidine and reduce the incidence of gag reflex. In addition, dexmedetomidine could prevent the increase in blood pressure and heart rate, salivation, and psychological emergence of reactions from ketamine. This study is in accordance with our study regarding the significant reduced incidence of intra- and post-operative adverse effects with the ketamine-dexmedetomidine group compared with the dexmedetomidine group.

### Table 4 Postoperative side effects in the two studied groups

| Variable | KD1 (n = 35) | D2 (n = 35) | P value |
|----------|--------------|-------------|---------|
| Discomfort, n (%) | 2 (5.7)* | 10 (28.6) | 0.02 |
| Gagging, n (%) | 1 (2.9)* | 8 (22.9) | 0.03 |
| Salivation, n (%) | 3 (8.6) | 1 (2.9) | 0.61 (NS) |

KD, ketamine-dexmedetomidine group, D2 dexmedetomidine group
*Significant; NS non-significant

### Table 5 Changes in parameters of liver functions (AST, ALT, and serum bilirubin) between before and 3 days after the procedure in the two studied groups

| Parameter | KD1 (n = 35) | D2 (n = 35) | P value |
|-----------|--------------|-------------|---------|
| AST (IU/L), mean ± SD | 89.3 ± 9.4 | 86.2 ± 9.1 | 0.17 (NS) |
| ALT (IU/L), mean ± SD | 77.9 ± 8.7 | 74.3 ± 8.3 | 0.08 (NS) |
| Bilirubin (mg/dl), mean ± SD | 52.3 ± 5.1 | 51.8 ± 4.9 | 0.68 (NS) |

KD, ketamine-dexmedetomidine group, D2 dexmedetomidine group
*Significant; NS non-significant

AST aspartate aminotransferase; ALT alanine aminotransferase

Demiraran et al. demonstrated that dexmedetomidine (loading dose of 1 μg/kg followed by an infusion of 0.2 μg/kg/hour was more effective than midazolam (0.07 mg to a maximum of 5 mg) during UGIE in adults (Demiraran et al., 2007).
Conclusions
The present study concluded that the use of a combination of ketamine and dexmedetomidine in UGIE procedures for hepatic patients is safe with a good recovery profile. There is no significant variation in hemodynamic parameters from the baseline. Endoscopic procedures could be performed with ease in almost all cases both endoscopist and patient satisfaction were excellent. Sedation and analgesia were adequate for the completion of the procedure with early recovery of the patients. There are no major adverse events like hypotension, bradycardia, gagging, discomfort, and respiratory depression. Both groups have no deleterious effects on liver function parameters.

Limitations
There is a need for further multicentric randomized controlled trials to confirm the findings of the present study so that the combination of ketamine and dexmedetomidine can become the standard of care for conscious sedation in short invasive procedures.

Abbreviations
ALT: Alanine transerase; ASA: American Society of Anesthesiologists; AST: Aspartate transerase; BIS: Bispectral index; D2: Dexmedetomidine alone group; ECG: Electrocardiography; HR: Heart rate; ICU: Intensive care unit; Ketodex: Ketamine-dexmedetomidine; KD: Ketamine-dexmedetomidine group; MAP: Mean arterial pressure; RR: Respiratory rate; RSS: Ramsay Sedation Scale; SD: Standard deviation; SPO2: Oxygen saturation; SPSS: Statistical Package for Social Science; VAS: Visual analogue score

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Authors’ contributions
HS: Analyzed and interpreted patient data, performed data collection tabulation, shared writing and revision of manuscript. OH: shared writing and revision of manuscript. HS: Analyzed and interpreted patient data, performed data collection. OH: shared writing and revision of manuscript. HS: Analyzed and interpreted patient data, performed data collection. OH: shared writing and revision of manuscript. HS: Analyzed and interpreted patient data, performed data collection. OH: shared writing and revision of manuscript. HS: Analyzed and interpreted patient data, performed data collection. OH: shared writing and revision of manuscript.

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Availability of data and materials
The datasets generated and analyzed during the current study are available from the corresponding author.

Declarations
Ethics approval and consent to participate
Ethical committee approval was obtained from Qena University Hospitals Institutional Review Board on 5 December 2016 and written informed consent was obtained from every patient participating in the study. The committee reference number is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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