Pain control using pethidine in combination with diazepam compared to diclofenac in combination with hyoscine-n-butyl bromide: in patients undergoing extracorporeal shock wave lithotripsy

Aslan Demir, Kursat Cecen, Mert Ali Karadag, Mehmet Uslu, Omer Erkam Arslan

Kafkas University, Medical School, Department of Urology, Kars, Turkey

Citation: Demir A, Cecen K, Karadag MA, Uslu M, Arslan OE. Pain control using pethidine in combination with diazepam compared to diclofenac in combination with hyoscine-n-butyl bromide in patients undergoing extracorporeal shock wave lithotripsy. Cent European J Urol. 2015; 68: 201-206.

Introduction Extracorporeal Shock Wave Lithotripsy (ESWL) remains the preferred least invasive treatment for urinary tract stones. The main purpose of this study was to compare two treatment modalities for pain control during the ESWL procedure.

Material and methods From 2013 to 2014, 220 patients received ESWL for kidney stones. Before the procedure, the weight and height were measured to determine the body mass index (BMI); in addition, oxygen saturation and the pulse of the patients, as well as pain level were determined. The pain control provided included two different methods: diclofenac sodium plus hyoscine-N-butyl bromide in the first group and pethidine plus diazepam in the second group. The pain level of the patients was determined using two different scales: the Wong-Baker and the Visual Analogue scales (VAS). At the end of three sessions, all patients were evaluated for the stone fragmentation rate by plain abdominal X-ray, and the findings were recorded and analyzed.

Results A total of 220 patients were enrolled in this study. There were 91 patients in the first group (diclofenac sodium + hyoscine-N-butyl bromide) (male/female: 63/28) and 129 (male/female: 83/46) patients in the second group (pethidine HCL +diazepam). The mean age with SD according to each group was 42.03 (±16.43) and 42.56 (±14.23), respectively (p = 0.8). With regard to pain scores (using the Wong-Baker and VAS scales), the responses were significantly lower in the second group (p <0.001).

Conclusions Pethidine in combination with diazepam was superior to diclofenac and Hyoscine-N-butyl bromide for pain in patients undergoing ESWL.

Key Words: extracorporeal shock wave lithotripsy ◦ sedation ◦ analgesia

INTRODUCTION

The first non-invasive treatment for urinary stones, developed in 1980 [1] was Extracorporeal Shock Wave Lithotripsy (ESWL). To this day, ESWL remains the least invasive treatment for urinary stones and is considered the preferred treatment for the majority of urinary stones, especially those of the kidneys. More than 90% of urinary stones in adults might be suitable for ESWL, but the number of ESWL procedures is lowering in the era of flexible ureterorenoscopy and percutaneous nephrolithotomy [2]. The introduction of affordable multifunctional lithotripters has made the ESWL available to increasingly more urology departments worldwide. However, pain control during the ESWL procedure remains a problem. Several anesthesia techniques have been used to provide sedation and analgesia [3]. Some of the analge-
sic drugs administered for the ESWL, however, carry the risk of respiratory depression, delayed discharge, and/or require unplanned hospital admission [4]. Since 2013, pethidine in combination with diazepam and diclofenac sodium in combination with hyoscine-N-butyl bromide combinations have been standard analgesia for patients who underwent ESWL in our department. Due to this reason, we would like to compare these 2 combinations. The main purpose of this study was to compare two treatment modalities for pain control during the ESWL procedure.

MATERIAL AND METHODS

This study was designed as a non-randomized prospective study and approved by the local ethics committee of our institution and performed in accordance with the Helsinki Declaration of the World Medical Association. Informed consent was obtained from all patients prior to ESWL procedure. An electrohydraulic device (Spark Gap Technology, ELMED™ lithotripsy systems, Ankara, Turkey) was used. Between 2013 and 2014, a total of 220 patients received ESWL for kidney stones that were between 42 and 200 mm². Stone burden was calculated by multiplying the longest horizontal and vertical axis of the stone viewed on plain film. A maximum of 3000 shocks were applied at 80 shocks per minute during each session or until complete disintegration of the stones. We measured oxygen saturation by pulse probe (pulse oximeter) that can be applied to the thumb of the patients. The main reason for using the pulse oximeter was to observe the changes in oxygen saturations which can be the result of respiratory depression, one of the side effects of pethidine. The pain control provided during the procedure included two different methods: diclofenac sodium in combination with hyoscine-N-butyl bromide was administered to the first group and pethidine in combination with diazepam was administered to the second group.

One hour before the procedure, diclofenac sodium (75 mg/kg) was administered IM, and Hyoscine-N-butyl bromide (20 mg/kg) was administered by IV infusion during the procedure in the first group. In the second group, one hour before the procedure, pethidine (1 mg/kg) was administered IM, and diazepam (10 mg) infusion was provided during the procedure. During the procedure, the oxygen saturation and pulse of the patients were measured and recorded. The side effects of the administered drugs including nausea, vomiting, allergic reactions, and dizziness were recorded by an ESWL nurse who was educated beforehand about the side effects of the drugs in our study.

The pain level of the patients at the end of the ESWL procedure was determined using two different scales (in order to increase the accuracy of pain level): the Wong-Baker and the Visual Analogue scales (VAS). The pain assessment scores were recorded. The Wong-Baker scale is used for pain assessment with six different face forms that are scored on a scale from 0 (no pain) to 5 (worst possible pain) (Figure 1). The VAS is used for pain assessment with a visual image of a straight line 10 cm in length that is scored from 0 (no pain) to 10 (worst possible pain). The patient was asked to mark the pain level at a point on the straight line (Figure 2). Patient comfort was determined by asking the following question: ‘Would the patient repeat the procedure without any chang-

Figure 1. The Wong-Baker Faces Pain Rating Scale.
es?’. The meaning of ‘tolerability’ in our study was finishing the procedure with the administered drugs. The observer answered the question ‘Did the patient finish the procedure?’. If the patient tolerated the pain until the end of the procedure, then the possible answer was ‘Yes’, and if not, ‘No, not tolerated’. At the end of three sessions, all patients were evaluated for the stone fragmentation rate, by plain abdominal X-ray, and the findings were recorded and analyzed. From the beginning of the procedure, all patients were followed-up by a nurse for pulse and blood pressure monitoring and presence of side effects such as: nausea, vomiting, dizziness, and respiratory depression.

**Statistical analysis**

Results are presented as the mean ± Standard deviation (SD). Data were analyzed using SPSS-16.0 for Windows (SPSS, Inc., Chicago, IL USA). Statistical analyses of the means of continuous variables were performed with the Student’s t-test and Mann-Whitney test. Categorical variables were analyzed using chi-square tests. Bivariate, multivariate, regression model and the Pearson Correlation Tests were used for correlation among variables. A probability level of p < 0.05 was considered significant.

**RESULTS**

A total of 220 patients were enrolled in this study. There were 91 patients in the first group (diclofenac sodium + hyoscine-N-butyl bromide) (male/female: 63/28) and 129 (male/female: 83/46) patients in the second group (pethidine HCL + diazepam). The mean age with the SD according to the groups was 42.03 (±16.43) and 42.56 (±14.23), respectively (p = 0.8). The demographic characteristics of two groups are summarized in Table 1a. The findings of the study with standard deviations are summarized in Table 1b.

| Group 1 n=91 | Group 2 n=129 | p |
|-------------|---------------|---|
| Age         | 42.03±16.43   | 42.56±14.23 | 0.8 |
| Gender (male/female) | 63/28 | 83/46 |
| BMI         | 25.8±3.46     | 26.1±4.07   | 0.5 |
| Stone size (mm²) | 115.88±32.15 | 116.26±39.91 | 0.9 |

There were no statistical differences between the groups with regard to values of oxygen saturation and pulse before the ESWL procedure. However, the values at the end of the procedure were lower in the second group. The difference between groups with regard to oxygen saturation was not significant (p = 0.06); however, the difference in pulse rate was significant (p < 0.001). The responses to the two questions, as noted previously, were higher in the second group (p < 0.001) (Table 1b).

With regard to the pain scores, the responses were significantly lower in the second group (p < 0.001). The mean values and SD are shown in Table 2. There was no statistical difference between groups in terms of stone size (p = 0.94, 115.88±32.156 mm² 116.26 ±39.91 mm² for group 1 and 2, respectively).
The fragmentation rates during the first sessions were higher in the second group \( (p = 0.01) \) (Table 2). There was no significant difference with regard to vomiting; however, the nausea rates were higher in the first group \( (p = 0.02) \) (Table 1b). The pain scale scores showed no significant differences with regard to gender (Wong-Baker scale \( p = 0.06 \), VAS scale \( p = 0.3 \)) (Table 3). There was no correlation between the BMI and pain scale scores according to groups (Pearson correlation value: \( 1, p = 0.93 \)). In addition, there was no correlation between stone size and the pain scale scores (Pearson correlation value: \( 0.03, p = 0.6 \)). There was a positive correlation between age and both of the pain scale scores (Pearson correlation value: \( 0.148, p = 0.02 \) for scale 1, and the Pearson correlation value: \( 0.13, p = 0.04 \), for scale 2). We found that pain control methods had an effect on VAS score and fragmentation rate of the stones with multivariate analysis (\( p = 0.000 \) and \( p = 0.012 \), respectively and adjusted R squared were \( 0.627 \) and \( 0.024 \), respectively). BMI had no effect on VAS score and fragmentation rate \( (p = 0.727 \) and \( p = 0.166 \), respectively) (Table 2).

There was no significant dizziness, respiratory depression or hypotension noted in any of the patients.

**DISCUSSION**

The noninvasive ESWL has become the procedure of choice for treatment of urinary system stones [5]. This is of special importance for those patients who cannot tolerate anesthesia. The development of second and third generation lithotripters has eliminated the limitations associated with the Dornier HM-3 (water bath, anesthesia). Simultaneously, the new development of endoscopic approaches (flexible ureteroscopes, holmium laser) has made endoscopic stone procedures less traumatic and an attractive choice because of the higher primary success rate. However, the procedure remains an invasive one that requires general anesthesia [5]. Most patients with urinary stones in Turkey and developed countries prefer the ESWL as first line management due to the complication potential associated with anesthesia [6, 7].

ESWL stone-free (SF) rates, for stones less than 2 cm, vary widely from 55% to 90% [8]. Many factors influence ESWL success rates, including the type of lithotripter used, patient characteristics such as BMI and age, as well as stone characteristics, such as size, location and hardness [8], any anatomic abnormalities related to the kidneys, and patient comfort during the procedure [2]. Also, Pettenati et al., showed that the presence of a double J stent affected the efficacy of ESWL in the treatment of lumbar ureteral stones. According to their study, logistic regression analysis revealed a higher failure rate when a double j stent was associated with a stone >8 mm [9]. Chaussy and Thuroff showed that the need for analgesia during the ESWL depends on the lithotripter used, the stone location, age, gender, and the number of shock waves performed [10]. According to the results of this study, the pain scores were higher in women; however, this difference was not statistically significant \( (p = 0.06 \) for scale 1 and \( p = 0.3 \) for scale 2) (Table 3). There was no correlation between the two groups with regard to BMI and stone size. However, there was a positive correlation between age and the pain scale scores in this study (Pearson correlation value: \( 0.148, P = 0.02 \)). Younger patients tolerated the procedures better than older ones; but this correlation was found to be weak.

The newer generations of lithotripters are associated with less pain. Thus, the preference for anesthesia during ESWL has progressively shifted from general anesthesia to sedation [11], except for special situations depending on the patient. Combinations of a sedative hypnotic and opioid analgesic are frequently used to provide patient comfort [11]. According to the European Association of Urology guidelines for urolithiasis, suitable analgesia is recommended because of its effect on treatment results by limiting pain-induced movements and excessive respiratory excursions [2] as well as improving patients’ comfort. It is well known that acute pain results in shortness of breath and an increase in ventilation [13]. Accord-

**Table 2. The results of multivariate analysis**

|                           | Pain score |     | Fragmentation |     |
|---------------------------|------------|-----|---------------|-----|
| **Adjusted R squared**    |            |     |               |     |
| Pain Control Method       | 0.627      | 0.000* | 0.024         | 0.012* |
| Age                       | 0.014      | 0.045* | -0.001        | 0.405  |
| BMI                       | -0.004     | 0.727  | 0.004         | 0.166  |
| Stone size                | -0.004     | 0.889  | 0.073         | 0.000* |

*p<0.05 significant

**Table 3. The pain scores according to gender (mean values with SD)**

| Pain scales               | Male Score | Female Score | p     |
|---------------------------|------------|--------------|-------|
| Wong-Baker Scale Scores   | 2.05 ±1.34 | 2.39 ±1.28   | 0.06  |
| Visual Analogue Scale     | 3.88 ±2.72 | 4.28 ±2.8    | 0.3   |

p<0.05 significant
ing to the report of Borgbjerg et al., experimental pain stimulates respiration [14]. According to our observation during ESWL, the kidney can mobilize about 2–4 cm depending on the depth of respiration. This finding can be associated with the degree of the perception of pain during the ESWL. For example, in situations without good pain control, the number of shock waves focused on the stone decrease resulting in a lower fragmentation rate during the first session. The results of this study showed that the fragmentation rate in the second group (pethidine + diazepam) was higher than the first group (diclofenac + hyoscine-N-butyl bromide) (p = 0.01) (Table 2). The use of diazepam likely reduced the depth of respiration by decreasing the patient’s anxiety and pain. Therefore, reduced perception of pain during the ESWL is essential for targeting and optimal fragmentation of stones during the ESWL [12]. According to the EAU guidelines on urolithiasis, careful control of pain during treatment is necessary to limit pain-induced movements of patients during the ESWL procedure [2]. Patients can move in response to strong shock waves. When the patient moves, retargeting of the urinary stones is required. Diazepam used in the second group reduced patient movement during the ESWL procedure by providing the patient with sedation and relaxation. This approach improved the fragmentation rate of stones (Table 2).

Various analgesic agents including opioids (morphine, pethidine and fentanyl), nonsteroidal anti-inflammatory drugs (NSAIDs-diclofenac, propofol, ketorolac, and piroxicam), local anesthetic agents and a number of combinations have been used during the ESWL by various techniques such as general anesthesia, subcutaneous and intravenous injections, patient-controlled analgesia, and monitored anesthesia care. Cutaneous creams such as a eutectic mixture of local anesthesia (EMLA) whether used alone or in combination with oral NSAIDs have also been used and can reduce analgesic requirements. Topical application of a combination of dimethyl sulfoxide and lidocaine has also been found to be effective [12]. According to the results of these studies, pain-control has been provided. While choosing the most suitable analgesic, one of the most important issues is to decrease patient anxiety and provide comfort so that repetitive sessions of ESWL can be provided in cases where residual stone fragments need additional sessions. One of the reasons for adding a benzodiazepine, in this study, was to decrease the anxiety and perception of pain among patients. Mazdak et al. used pethidine for pain-control during the ESWL and the pain scores of their patients was 4.11 ±1.69 on the VAS. The results of this study showed that the score could be reduced about two points, with the same pain scale, by combining pethidine and diazepam. According to the results of this study, the rate of additional sessions because of residual fragments was higher in the second group when compared to the first group; the difference between groups was significant statistically (p <0.001) (Table 2). This result may be associated with the good pain-control in the second group during ESWL.

Although opioids provide effective analgesia, they are associated with significant complications such as respiratory depression, bradycardia, hypotension, nausea, vomiting, and an extended monitoring time [12]. According to the results of this study, the nausea rates were 47.3% and 32.6% for groups 1 and 2, respectively (p = 0.02) (Table 1b). This was associated with the colic pain that occurred during the ESWL; likely due to mobilization of the stone fragments in the kidney. The sedation provided by diazepam in the second group reduced the nausea rates compared to the first group; however, there was no difference in vomiting between the two study groups. There were no other serious complications. There were no differences between groups before the procedure, but after the procedure, although there was no difference in the blood oxygen saturation, the pulse rate was lower in the second group compared to the first group (p <0.001) (Table 1b). This finding was likely due to the effects of diazepam.

Limitations of the study

We did not obtain a cut-off value on pain level with our data and we could not analyse the effect of double J stents on the treatment of stones with ESWL due to the sizes of the kidney stones in our study (less than 2 cm). As is the routine for our department, we do not prefer to insert double J stents prior to the ESWL in patients having stones less than 2 cm. We think that if they were included in the study, the results would be more significant.

CONCLUSIONS

The results of this study showed that a pethidine combination with diazepam was superior to diclofenac in combination with hyoscine-N-butyl bromide. By providing good analgesia and sedation, patient comfort was improved during the ESWL procedure. As a result, the fragmentation rates and need for additional sessions to deal with fragments or hard stones were increased. Many types of analgesia have been applied by various techniques by urologists,
excluding general anesthesia and deep sedation, however, there are no guidelines for pain-control. Additional studies are needed to determine the safest and most effective analgesia with regard to side effects, discharge time, easy usage (for urologists), and cost in patients undergoing the ESWL procedure. The ideal analgesic that would offer optimal pain control, minimal side effects, and cost-effectiveness remains to be determined. Opioids administered using various techniques, provide effective analgesia, but they require active monitoring of the patient and have potential adverse effects.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS
The data of our study were presented in the Turkish Urology Congress 2014. We would like to thank Murat Bagcioglu, MD due his support for preparing Turkish abstract for this congress.

References

1. Doré B. Extracorporeal shock wave lithotripsy (ESWL) procedure in urology. Ann Urol. 2005; 39: 137-158.
2. Türk C, Knoll T, Petrak A, Sarica K, Straub M, Seitz C. EAU guidelines on Urolithiasis. European Association of Urology 2012; p. 28.
3. Mazdak H, Abazari P, Ghassami F, Najafipour S. The analgesic effect of inhalational Entonox for extracorporeal shock wave lithotripsy. Urol Res. 2007; 35: 331-334.
4. Alhashemi JA, Kaki AM. Dexmedetomidine in combination with morphine PCA provides superior analgesia for shock wave lithotripsy. Can J Anesth. 2004; 51: 342-347.
5. Christian C, Thorsten B. The preferred treatment for upper tract stones is extracorporeal shock wave lithotripsy (ESWL) or ureteroscopic: pro ESWL. Urology. 2005; 74: 259-262.
6. Karadag MA, Demir A, Cecen K, et al. Flexible Ureterorenoscopy versus semingid ureteroscopy for the treatment of proximal ureteral stones: A retrospective comparative analysis of 124 patients. Urol J. 2014; 11: 1867-1872.
7. Segura JW, Preminger GM, Assimos DG, et al. Ureteral Stones Clinical Guidelines panel summary report on the management of ureteral calculi. The American Urological Association. J Urol. 1997; 158: 1915-1921.
8. Weld KJ, Montiglio C, Morris MS, Bush AC, Cespedes DR. Shock wave lithotripsy succes for renal stones based on patient and stone computed tomography characteristics. Urology. 2005; 70: 1043-1046.
9. Pettenati C, El Fegoun AB, Hupertan V, Dominique S, Ravery V. Double J stent reduces the efficacy of extracorporeal shock wave lithotripsy in the treatment of lumbar ureteral stones. Cent European J Urol. 2013; 66: 309-313.
10. Chaussy C, Thuroff S. Pain sensitivity in ESWL patients. Does every stone location need the same analgesia management? J Urol. 1996; suppl 159: 541.
11. Kaygusuz K, Gokce G, Gursoy S, Ayan S, Mimaroglu C, Gultekin Y. A comparison of sedation with dexmedetomidine or propofol during shockwave lithotripsy: a randomized controlled trial. Anesth Analg. 2008; 106: 114-119.
12. Gupta NP, Kumar A. Analgesia for pain control during extracorporeal shock wave lithotripsy: Current status. Indian J Urol. 2008; 24: 155-158.
13. Wilhelm FH, Gevirtz R, Roth WT. Respiratory dysregulation in anxiety, functional cardiac, and pain disorders. Behav Modif. 2001; 25: 513-545.
14. Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain. 1996; 64: 123-128.