Local anesthetics versus systemic analgesics for reducing pain during Extracorporeal Shock Wave Lithotripsy (ESWL): A systematic review and meta-analysis

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Abstract

Extracorporeal Shock Wave Lithotripsy (ESWL) is one of the treatment options for patients with renal and ureteral calculi. Even though the procedure is less invasive compared to others, pain caused by the procedure is a major concern. Several studies recommended the use of either local or systemic analgesia with varying results. We aimed to compare the use of local anesthetics and systemic analgesics from randomized controlled trials evaluating pain management during ESWL. A systematic search adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol was performed in the Medline, ScienceDirect, and Cochrane library databases. The bias was evaluated using the Cochrane risk of bias tool. Mean difference (MD) was used to analyze continuous outcomes. A total of seven studies were obtained. The topical anesthesia used was eutectic mixture of local anesthetic cream and xylocaine gel. In contrast, the local injection anesthesia used was subcutaneous prilocaine and intracutaneous sterile water injection. The systemic analgesics used were intramuscular and oral forms of sodium diclofenac. There is no significant difference between the visual analogue scale results between the local and systemic groups ($P > .05$). The differences in ESWL frequency were also insignificant ($P > .05$). Additional analgesics supplementation (MD 8.44, 95% CI 2.28-14.61, $P = .007$) and the duration of the procedure (MD 1.39, 95% CI 0.21-2.56, $P = .02$) were significantly lower in the local group. Local anesthesia in ESWL shows a similar degree of pain and frequency but has a shorter duration and fewer analgesics supplementation than systemic analgesics.

Keywords: Analgesics; anesthesia; extracorporeal shockwave therapy; lithotripsy; ureterolithiasis; urolithiasis.

Introduction

Urolithiasis, commonly known as urinary stones or calculi, is one of the most commonly encountered urological problems, affecting approximately two to three percent of the general population with a 50% lifetime recurrence rate.1 Current management of choice for urolithiasis is divided into conservative and surgical managements based on multiple factors, such as stone characteristics, patient profile, and the availability of modalities.2 Large stones with major symptomatic manifestations or complications often require active stone removal.3 The advancements in medical technology have pushed minimally invasive approaches, such as endoscopic surgery and Extracorporeal Shock Wave Lithotripsy (ESWL), for urolithiasis management to the mainstream.4 Since it was first introduced in the 1980s, ESWL has become one of the first-line therapy options for most patients with renal and ureteral calculi less than 20 mm in size.5 Even though the procedure is considered less invasive than other alternatives, pain caused by shockwaves reaching superficial and deep structures is still a major concern.6 Several factors are associated with the
procedure responsible for inducing pain, including size and location of the stone, cavitation effects, focal zone size, shockwave peak pressure, among many others. In addition to being a cause of morbidity, pain could affect the procedure’s outcomes due to movements and excessive breathing, impeding focus on the stone during the procedure. Pain intensity may also limit a sufficient dose of energy that could be given to the patient. In the early days, the procedure was usually performed under general anesthesia. The technological improvements and modifications of machines have simplified the procedure, thus reducing the pain due to lithotripsy. However, despite these advancements, many patients still require analgesia. Nowadays, recommended drugs for pain management include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol, and local alternatives. Local anesthetics have several advantages over systemic alternatives, especially regarding minimal systemic side effects and ease of administration. Even though the European Association of Urology (EAU) guideline highlights the importance of pain management during ESWL, a specific type of painkiller has yet to be determined. Several studies have attempted to compare local and systemic alternatives with varying results. Therefore, in this systematic review, we aimed to compare local anesthetic and systemic analgesics for reducing pain in patients undergoing ESWL.

Material and Methods

Study Design
This systematic review was conducted according to the Cochrane Handbook for Systematic Review for Interventions and Preferred Reporting Items for Systematic Review and Meta-Analysis. This study has been registered in the PROSPERO public database (CRD42020211170).

Systematic Search Strategy
The computerized data search was conducted from November 2020 until February 28, 2021 by all authors through Medline, ScienceDirect, and Cochrane library. The keyword used in this study consists of [(“lithotripsy” OR “lithotripsy” OR (“extracorporeal” AND “shock” AND “wave” AND “lithotripsy”) OR “extracorporeal shock wave lithotripsy” OR “ESWL”) AND (“analgesia” OR “anesthesia” OR “analgesics”)] OR (“pain” OR “pain”) AND (“urinary calculi” OR (“urinary” AND “calculi”) OR “urinary calculi” OR (“urinary” AND “stone”) OR “urinary stone”). We also investigated references within the identified articles to avoid missing potential studies. Conference proceedings of the EAU were also searched.

Eligibility Criteria
This review comprised of randomized controlled trials (RCTs) and prospective studies. All studies following these criteria were in the following analysis: (1) adult patients with urinary stone undergoing ESWL, (2) studies with the comparison of local and systemic analgesics during ESWL, (3) the primary outcomes were visual analogue scale (VAS), additional analgesics used, frequency of ESWL shocks, ESWL voltage, and ESWL duration, and (4) the secondary outcomes were the need of analgesic supplementation and voltage of ESWL shockwave throughout the operation. The timing for reported VAS was collected after ESWL was nearly finished. Exclusion criteria were abstract only, animal studies, a combination of local anesthesia and systemic analgesics, a combination of ESWL with other urinary stone treatment methods, and a study that used non-VAS parameters of pain perceptions. In the case of insufficient pain control during the procedure, intravenous painkillers such as fentanyl and pethidine were given for additional analgesic supplementation. These circumstances will be used as secondary parameters in this study.

Data Synthesis and Quality Assessment
Study selection and data extraction process were performed by two different authors independently. Any disagreement in selecting eligible articles and data tabulation was discussed with other authors who are experts in the area. Two authors also assessed each article’s bias using Cochrane risk of bias (ROB) tools for RCT. Any variance in the decision was discussed further with other authors until an agreement was met.

Statistical Analysis
This study used the Review Manager software, version 5.4 (Cochrane Collaboration, Oxford, UK), to perform data analysis in forest plot models. The I² and P-value were applied to assess the heterogeneity of each pooled analysis. Random-
effects models were used for studies with high heterogeneity ($P < .1, I^2 > 50\%$), and fixed-effects models were used for studies without no or small heterogeneity ($P > .1, I^2 < 50\%$). The estimated analysis of parameters in this study was continuous data with the mean difference (MD) to evaluate the outcomes.

**Results**

**Overview of Literature Search**

During the initial search, 496 studies were identified with 97 duplications, as shown in Figure 1. After the duplicates were removed, there were 399 articles screened based on title, keywords, and abstract. Finally, seven studies met the criteria for quantitative analysis or meta-analysis after excluding 17 studies. The total number of samples from the seven included studies was 1,065 patients, 476 in the local anesthesia treatment group and 589 in the systemic analgesics group. The baseline characteristic of each eligible study was shown in Table 1. The local anesthesia used in the studies consisted of topical and injection. The regimen of topical anesthesia was a eutectic mixture of local anesthetic cream (EMLA) and xylocaaine gel. In contrast, the local injection anesthesia was subcutaneous prilocaine (SC) and intracutaneous sterile water injection (ISWI). The systemic analgesics were NSAIDs, consisting of both intramuscular (IM) and oral forms of sodium...
diclofenac and ketorolac injections. There were two types of lithotripter used: third generation electrohydraulic lithotripter and Dornier delta compact lithotripter. The average age of the subjects was 37.5-46.9 years old in the local group and 37.6-45.9 years in the systemic group. Stone sizes vary from 9.44 to 33 mm in the local group and 9.26 to 45 mm in the systemic group. Based on the Cochrane ROB tool in Figure 2, most studies portrayed a low risk of bias, except an unclear risk of bias in selection performance and detection section, shown in Figure 2. After the randomization process, the allocation results should not be conveyed to the patient to minimize the possibility of bias due to placebo. However, allocation concealment was only mentioned in two studies.

**VAS During ESWL**

Seven RCT reported the mean VAS during ESWL procedures with a total of 1,065 patients in Figure 3.10,15–20 Four from the seven RCTs compared EMLA cream and systemic NSAID. We performed a subgroup analysis in the forest plot to evaluate specifically between them. Comparing EMLA and systemic analgesics using random-effects models showed no significant difference (MD –0.07, 95% CI –0.76 to 0.63, \( P = .85 \)). Other methods of local anesthesia consist of infiltration of subcutaneous prilocaine, application of topical lidocaine gel, and ISWI. Comparisons between other local anesthesia methods and systemic analgesics on the other three RCTs also showed no significant difference in the mean VAS (MD –1.23, 95% CI –2.93 to 0.47, \( P = .16 \)). Total comparisons of two methods representing the usage between local anesthesia and systemic analgesics administration did not show significant results (MD –0.46, 95% CI –1.03 to 0.10, \( P = .11 \)). All analyses were conducted using the random-effects models due to a high heterogeneity (\( I^2 > 50\% \)).

**Additional Analgesics Supplementation**

Two RCTs in Figure 4 reported the need for analgesic supplementation during ESWL with a total of 164 patients. Plot analysis showed that there was significance difference, in which systemic anesthesia requires additional analgesic supplementation (MD 8.44, 95% CI 2.28-14.61, \( P < .007 \)). Random effects model was used as there were high heterogeneity (\( I^2 = 89\% \)).

**Frequency of ESWL Shocks**

Seven RCTs reported the number of ESWL shockwave with a total of 1,065 patients, as shown in Figure 4. There was no significance MDs in ESWL shocks between local and systemic anesthesia group (MD 83.44; 95% CI 37.23-204.10, \( P = .18 \)). A random-effects model was used due to high heterogeneity (\( I^2 = 96\% \)).

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**Table 1. Baseline Characteristic of Included Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Sample size (n)</th>
<th>Type of intervention</th>
<th>Sample (n) based on anesthesia</th>
<th>Age (years)</th>
<th>BMI (kg m(^{-2}))</th>
<th>Stone size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basar et al.</td>
<td>RCT</td>
<td>50</td>
<td>EMLA cream and diclofenac injection</td>
<td>Local: 25</td>
<td>46.60 ± 2.55</td>
<td>39.95 ± 2.79</td>
<td>9.69 ± 3.57</td>
</tr>
<tr>
<td>Yilmaz et al.</td>
<td>RCT</td>
<td>114</td>
<td>Prilocain SC and diclofenac injection</td>
<td>Local: 56</td>
<td>42.23 ± 12.04</td>
<td>40.59 ± 11.96</td>
<td>10.29 ± 2.35</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>RCT</td>
<td>160</td>
<td>EMLA cream and diclofenac oral</td>
<td>Local: 80</td>
<td>37.5 ± 5.26</td>
<td>37.6 ± 4.75</td>
<td>26.2 ± 2.13</td>
</tr>
<tr>
<td>Eryıldırım et al.</td>
<td>RCT</td>
<td>80</td>
<td>EMLA cream and diclofenac oral</td>
<td>Local: 40</td>
<td>44.4 ± 1.9</td>
<td>43.6 ± 1.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu and Zang</td>
<td>RCT</td>
<td>69</td>
<td>EMLA cream and diclofenac injection</td>
<td>Local: 34</td>
<td>37.5 ± 13.5</td>
<td>38.5 ± 12.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Hashem et al.</td>
<td>RCT</td>
<td>82</td>
<td>Xylocain gel and ketorolac injection</td>
<td>Local: 29</td>
<td>46.9 ± 11.7</td>
<td>45.9 ± 12.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Gül and Gal</td>
<td>RCT</td>
<td>510</td>
<td>ISWI and diclofenac injection</td>
<td>Local: 212</td>
<td>41.2 ± 9.4</td>
<td>39.9 ± 10.1</td>
<td>14.8 ± 2.8</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomized controlled trial; ISWI, intracutaneous sterile water injection; N/A, not available.
ESWL Duration
Six RCTs reported the outcome of ESWL durations with a total of 954 patients in Figure 4. There was a significant difference where local anesthesia displayed a shorter duration for the ESWL procedure (MD 1.39, 95% CI –0.21 to 2.56, \(P = .02\)). Heterogeneity among the studies was significant in the pooled analysis (\(I^2 = 91\%\), \(P < .00001\)), thus a random-effects model was used.

ESWL Voltage
In Figure 4, five RCTs reported the average voltage during ESWL with a total of 404 patients. No significant difference
was displayed in the plot analysis (MD –0.34, 95% CI –0.89 to 0.21, P = .23). The random effects model was used as there was high heterogeneity (I² = 95%).

Discussion
The advantages of ESWL as the current treatment of choice for kidney and ureteral stones are its noninvasiveness and minimal side effects.21 One of the major benefits for the patient compared to other procedures is that this procedure does not require general anesthesia and can be performed in an outpatient setting. One of the main concerns of the procedure is pain or discomfort of the patient felt during the procedure, as apart from causing morbidity, pain could induce excessive body movement and respiratory rate. These could affect stone fragmentation, thus decreasing the stone-free rate. The increase in blood pressure due to pain might contribute to kidney hematoma.22

To compare the efficacy of different approaches to treat pain, it is necessary to evaluate pain scales and additional analgesics use. As painful sensations may affect the frequency, voltage, and duration of ESWL, determining the most optimal approach to manage pain is essential to increase treatment efficacy.23

Pain During ESWL
The use of local anesthesia in ESWL was introduced in the early 1990s.24 Several studies investigated the use of subcutaneous injection of lidocaine and its derivatives during this time. In 1991, a study evaluated the use of EMLA cream compared to placebo to manage pain during ESWL.25 A meta-analysis in 2020 concluded that the use of EMLA before the procedure could reduce pain.26 Various techniques of local anesthesia for ESWL have been proposed. The infiltrative injection of 20 mL prilocaine in the lumbar region was recommended by Yilmaz et al.27 in 2008. A study by Maldonado-Avila et al.28 in 2017 showed that local anesthesia by blocking the 12th subcostal nerve using 2% had similar efficacy in
reducing pain compared to combined analgesics. This systematic review divided the comparisons into two subgroups: one using EMLA cream as the local anesthesia and another using other analgesics such as ISWI and xylocaine gel injections. There is no significant MD of VAS between EMLA and systemic NSAIDs (MD –0.07, 95% CI –0.76 to 0.63, P = .85). EMLA cream is usually used for topical anesthesia in venous catheterization, condyloma acuminata excision, phimosis, and skin graft preparation. Even though there is no significant difference in pain intensity between applying EMLA and systemic NSAIDs, EMLA is easier to apply, noninvasive, and has minimal side effects. Comparing ISWI and xylocaine gel with systemic analgesics in this meta-analysis also showed no significant difference in mean VAS (MD –1.23, 95% CI –2.93 to 0.47, P = .16). Previous studies reported that ISWI had similar efficacy to natrium diclofenac injection, albeit with minimal to no side effects. ISWI is also safe, cheap, and simple compared to systemic analgesics. In one RCT, the patient group receiving xylocaine gel had a higher mean VAS compared to the ketorolac injection group. However, in this study, xylocaine gel was given at the start of the procedure; thus, there is a possibility that maximal absorption had not been achieved. However, there is a higher amount of additional analgesics supplementation of the systemic group compared to the local group (MD 8.44, 95% CI 2.28-14.61, P < .007), indicating that one-time administration of the NSAID was not enough among the patients. Potential side effects due to NSAIDs, such as gastrointestinal issues, hypersensitivity reaction, and coagulative problems, should not be taken lightly.

**Frequency, Voltage, and Duration of ESWL**

Comparing frequency, voltage, and duration of ESWL is important to determine the analgesics of choice. Intense and unbearable pain may cause the operator to reduce the frequency of shots and the machine’s voltage, thus reducing its effectiveness. There was no significance MDs in ESWL shocks (MD 83.44; 95% CI –37.23 to 204.10, P = .18) and average voltage (MD –0.34, 95% CI –0.89 to 0.21, P = .23) between the local and systemic anesthesia group.

An ideal choice would support a sufficient frequency and voltage as low tolerance of pain may hinder the effective energy dose of ESWL. The insignificant difference in the frequency and voltage between the two groups showed that local anesthesia could replace systemic analgesics for pain management. The local anesthesia group also displayed a shorter duration for ESWL procedure (MD 1.39, 95% CI 0.21-2.56, P = .02). Unbearable pain during the procedure could increase patient movement causing the shockwaves to be out of focus, thus increasing the duration of the procedure. A shorter duration demonstrated that the patients in the local group could withstand pain compared to the systemic group. The patients in the systemic analgesic also received more analgesic supplementation, highlighting the advantage of local anesthetics even further. The overall results in this meta-analysis showed that local anesthesia could be given for patients undergoing ESWL with contraindications to systemic analgesics. Local anesthesia and systemic analgesics are comparable in reducing pain with similar frequency and energy of the procedure. Sufficient pain management allows for higher acoustic energy, thus increasing the success rate of stone fragmentation.

**Local versus Systemic in Other Procedures for Urolithiasis**

Pain management is also a concern in other urological procedures for stone management. A systematic review by Schembri et al. in 2020 showed the promise of local anesthetics as an alternative to general anesthesia for ureteroscopy. Several studies also investigated the role of local analgesics in postoperative pain control after percutaneous nephrolithotomy. A study by Tüzel et al. showed that single dose local anesthetic infiltration to the nephrostomy tract could reduce supplemental analgesics.

**Study Limitations and Future Suggestions**

This systematic review is limited by the interventions of the included RCTs, which have different dose and type of both the local anesthesia and systemic analgesics. Similar types classified into subgroups would answer a more specific comparison between two particular drugs. Moreover, the mean VAS results chosen for the analysis are the mean VAS nearing the end of the procedure. The value is considered representative of the patients’ overall pain during the procedure. Future studies could evaluate different sequential values of VAS throughout the procedure. Other alternatives for pain management should also be investigated in the future. In recent years, there is an increase in complementary medicine use during ESWL by urologists. A systematic review by Saraogi et al. concluded that complementary medicine might reduce analgesics and anxiolytics while increasing patient satisfaction during the procedure. Music, acupuncture, and transcutaneous electrical nerve stimulation are among the most popular alternatives used for ESWL, among which music has been shown to reduce anxiety among patients. These adjunct medicines currently lack substantial evidence supporting their efficacy, warranting further investigations regarding their use.

**Conclusion**

The use of local anesthesia in ESWL shows a similar degree of pain scale and number of shots. Still, it has a shorter ESWL
duration and fewer analgesics supplementation compared to systemic analgesics. Local anesthesia is a better pain management alternative than systemic analgesics, especially for patients with contraindications to systemic analgesics.

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**References**


