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Efficacy of Eutectic Mixture of Local Anesthetics on Pain Control During Extracorporeal Shock Wave Lithotripsy: A Systematic Review and Meta-Analysis

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Data Collection B
Statistical Analysis C
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Background: The efficacy of a eutectic mixture of local anesthetics (EMLA) for pain control in extracorporeal shock wave lithotripsy is unclear. The aim of this study was to assess the effect of EMLA cream on pain control during extracorporeal shock wave lithotripsy.

Material/Methods: We searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials to identify relevant randomized controlled trials that compared the pain control efficacies of EMLA *vs.* placebo.

Study eligibility criteria, participants, and interventions: Randomized controlled trials that compared the effect of EMLA with placebo cream for patients underwent extracorporeal shock wave lithotripsy.

Study appraisal and synthesis methods: Two review authors extracted data independently using a designed data extraction form and risk of bias by Cochrane Collaboration's tool.

Results: Nine studies, including 10 randomized controlled trials with 1167 patients, were eligible. The EMLA group experienced less pain (mean difference, –0.47; 95% confidence interval, –0.78 to –0.16; p=0.003) and shorter duration of lithotripsy (mean difference, –1.70, 95% confidence interval: –2.31 to –1.10, p<0.0001) than the placebo group. There were no significant differences in the number of patients who needed extra intravenous medication (p=0.610), number of patients with insufficient extracorporeal shock wave lithotripsy pain control (p=0.530), and number of patients with opioid adverse effects (p=0.320). Limitations: Long interval between the studies, different kinds of lithotripters.

Conclusions: EMLA can reduce pain during the ESWL procedure.

MeSH Keywords: Anesthetics • Lithotripsy • Pain

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Background

Extracorporeal shock wave lithotripsy (ESWL) is a very important treatment for renal and/or ureteral calculi [1–4], but pain control during this procedure needs further research. ESWL works by causing a direct shearing force and the formation of cavitation bubbles that rupture stones and reduce their size [2]. However, this procedure can be painful because the continuous shock waves act on cutaneous nociceptors, causing parietal pain. In addition, the elevated intrapelvic pressure and distention of the renal capsule act on visceral nociceptors, resulting in visceral pain. Moreover, the movement of stone fragments can cause colic pain [2,5–7].

Up to 40% of patients require analgesics to quell pain in the costovertebral angle and flank area [2,8]. Various agents can be used to achieve analgesia. General anesthesia, inhalation anesthesia, spinal anesthesia, infiltrating local anesthesia, dermal anesthesia, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain control in ESWL. Some studies have also used ISWI for pain management in the intracutaneous sterile water injection (ISWI) procedure [9]. Among them, dermal anesthesia, opioids, and NSAIDs are most commonly applied [6–8].

A eutectic mixture of local anesthetics (EMLA) is a type of drug for dermal anesthesia that is typically administered as a cream [10,11]. MLA contains lignocaine (2.5%) and prilocaine (2.5%) [12] that penetrate intact skin to the epidermal and dermal skin layers and function as local analgesics [13]. Several studies have discussed the effects of EMLA pain control during ESWL for urinary tract calculi. The efficacy of EMLA during ESWL is debatable [14–17].

The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to assess the effect of EMLA cream on pain control during ESWL and to clarify the real efficacy of EMLA for ESWL.

Material and Methods

Systematic search strategy

All studies published in English were searched in Medline, EMBASE, and the Cochrane Central Register of Controlled Trials. The research periods were between 1 Jan 1991 and 26 September 2019. The retrieval deadline was 26 September 2019. Search terms we used to identify all relevant studies are listed in the supplementary table. We also investigated references within the identified articles. Conference proceedings of the European Association of Urology and American Urological Association from 2011 to 2019 were also searched.

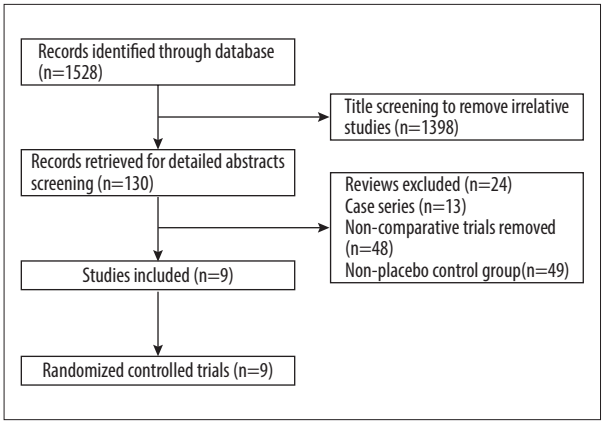

Figure 1. Flow diagram of the search process for eligible studies.

When several outcomes reported the same study, either the most recent or the most formal report was used.

Inclusion and exclusion criteria

All available RCTs that compared the effect of EMLA with that of placebo cream in ESWL were included. In case of insufficient pain control in the ESWL procedure, IV anesthetics, including fentanyl and pethidine, were used for supplementary pain control. Studies with outcomes that did not show standard deviations were excluded. In addition, patients who did not complete ESWL were also excluded. The PRISMA flow diagram is shown in Figure 1.

Data extraction

Two authors of this manuscript (Yu Huang and Shuaishuai Chai) extracted data independently by using a designed data extraction form. After extraction, both authors combined their data; discrepancies were resolved through discussion. A third author (Decai Wang) resolved discrepancies if the former reviewers could not reach an agreement.

Outcome

The primary outcome was the visual analog scale (VAS) score for pain during ESWL. Duration of ESWL, number of patients with insufficient pain control in ESWL procedure, number of patients who needed extra IV medication, and number of patients who experienced opioid adverse effects are identified as secondary outcomes. The VAS score was used to determine pain levels by the patients, who indicated a position along a continuous line between 2 end-points (0=no pain; 10=maximum possible pain). The number of patients with insufficient pain control in the ESWL procedure was defined as the number of patients who needed to use patient-controlled analgesia (PCA) devices for pain control or who felt severe pain in the ESWL procedure (VAS score ≥7) without PCA devices. Adverse effects of opioids mentioned by included articles were registered.

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Table 1. Basic features of included study.

Study (year)	Country	Design	No. of patients		Age (year)		Supplementary anesthetics		Generation of Lithotripter
			EMLA	Placebo	EMLA	Placebo	Agent	Timing	
Bierkens A.F. 1991 [13]	The Netherlands	RCT	40	43	50.6 (26–84)	48.5 (28–73)	Fentanyl	Only when needed	2
Acar A. 2013 [7]	Turkey	RCT	30	30	48.5±2.2	43.4±2.5	Remifentanil	Only when needed	NA
Gallego Vilar D. 2012 [6]	Spain	RCT	165	269	47.2±16.3	43.6±17.1	Pethidine	During the entire ESWL procedure	3
Yilmaz E. 2005 [5]	Turkey	RCT	23	22	43.3±11.73	39.04±11.27	Fentanyl	During the entire ESWL procedure	3
Tiselius H.G. 1993 [18]	Sweden	RCT	99	100	NA	NA	Meperidine	During the entire ESWL procedure	1
McDonald, P.F. 1992 [15]	Australia	RCT	30	30	NA	NA	Fentanyl	Only when needed	2
Ganapathy, S. 1996 [16]	Canada	RCT	44	39	47.1±11.6	47.4±12.3	Alfentanil	Only when needed	2
Monk, T.G. 1994 [11]	United States	RCT	30	29	53±12	50±13	Alfentanil	Only when needed	1
Tritrakarn, T. part 1 2000 [14]	Thailand	RCT	12	12	NA	NA	Fentanyl	Only when needed	3
Tritrakarn, T. part 2 2000 [14]	Thailand	RCT	39	41	38±11	41±10	NA	Only when needed	3

RCT – randomized controlled trial; EMLA – eutectic mixture of local anesthetics; ESWL – Extracorporeal Shock Wave Lithotripsy; NA – not applicable.

Quality assessment of included studies

Two independent reviewers (Yu Huang and Shuaishuai Chai) assessed the included articles using the Cochrane Collaboration tool for assessing risk of bias and the Quality of Reporting of Meta-analyses guidelines [18]. Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases were considered as our quality items.

Data analysis

We used Stata/SE 13.0 software (StataCorp LP, College Station, TX, USA) and Review Manager, version 5.2.0 (Cochrane Collaboration, Oxford, UK) to perform data analysis. The I^2 and χ^2 tests were applied to assess heterogeneity. We considered I^2 values of 25%, 50%, and 75% as low, medium, and high levels of heterogeneity, respectively. Random-effects models were used for studies with significant heterogeneity, and fixed-effects models were used for studies without significant heterogeneity. The mean difference (MD) was used to evaluate the continuous outcomes, and relative risk (RR) was used for dichotomous data. A p value <0.05 was taken to indicate statistical significance.

Results

Description of studies

According to the search strategies, 10 trials in 9 articles (2 separate trials were included in the article by Tritrakarn) with 1167 patients, were eligible from the databases for further analysis. One of those studies consisted of 2 separated trials, so we analyzed both trials in this review [5–7,12,14–17,19]. Among them, 7 trials used PCA devices as supplementary anesthesia if EMLA could not control the pain sufficiently during ESWL, and 3 trials used intravenous (IV) anesthetics in combination with EMLA during the ESWL procedure. Different drugs were administered in the PCA devices: fentanyl in 4 trials, alfentanil in 2, and remifentanil in 1. For IV infusion, 1 group prescribed fentanyl and 2 others prescribed pethidine. In these studies, 532 patients received EMLA and 635 received placebo during ESWL. Table 1 summarizes the baseline characteristics of those 10 trials.

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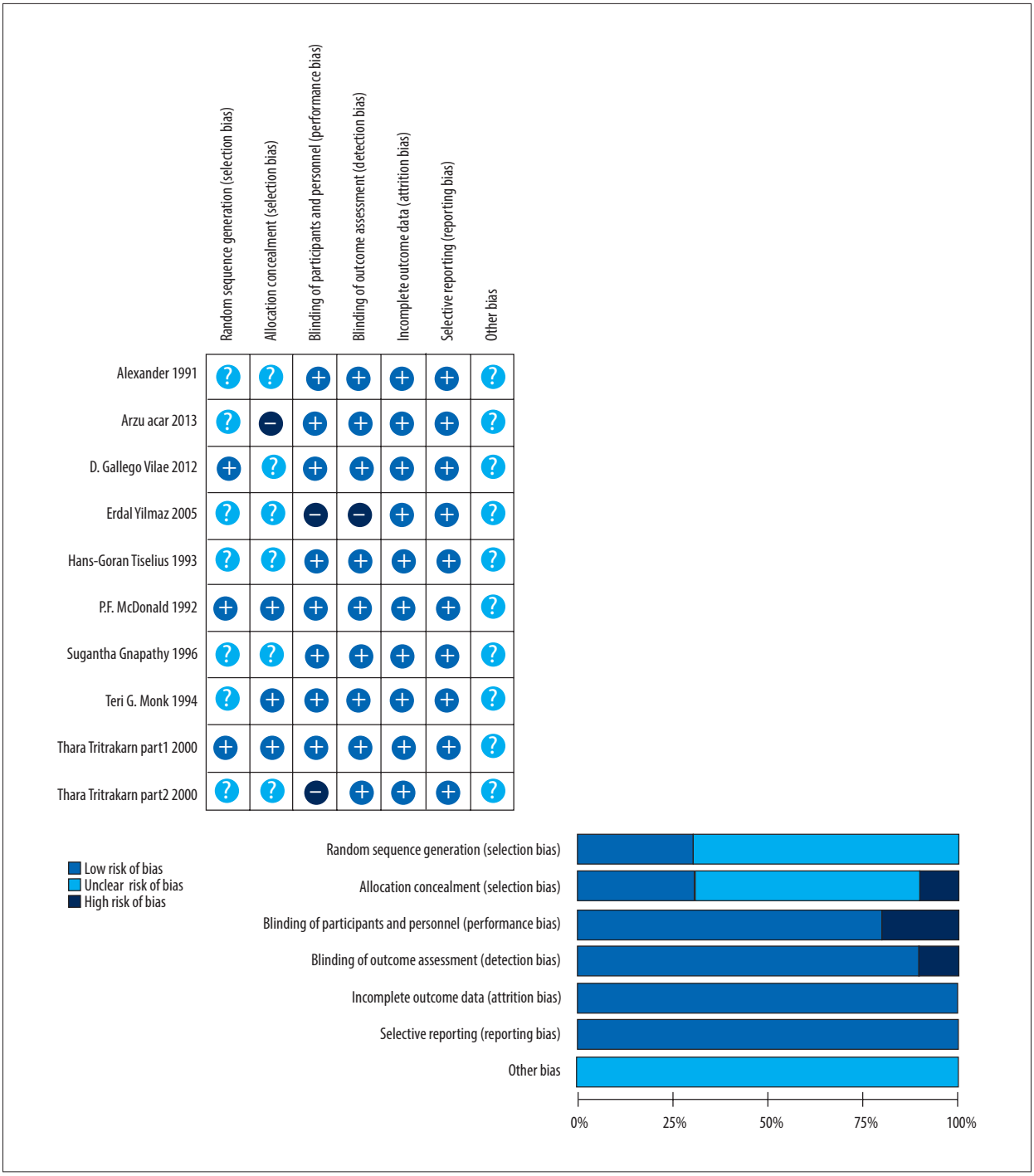

Figure 2. Risk of bias.

Risk of bias

The risk of bias of the included studies is shown in Figure 2. All trials declared that the patients were randomly allocated to 2 groups; however, 7 trials did not precisely describe the method of randomization. Only 3 trials described the details of concealed allocation. Nine out of 10 trials were double-blinded.

VAS score during ESWL procedure

Six trials, including 901 patients, reported VAS scores during the ESWL procedure. We chose the highest VAS score if the article reported more than 1 VAS score during the ESWL procedure.

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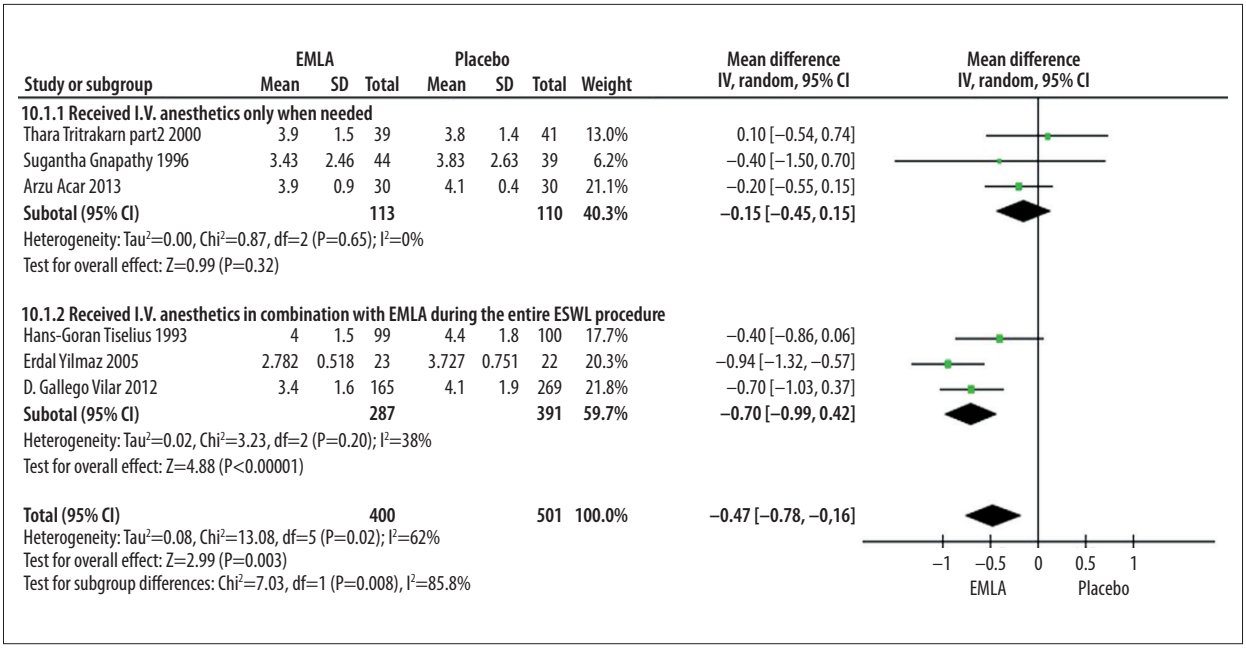

Figure 3. Forest plot analysis showing VAS score of pain during ESWL. a: Subgroups according to whether IV anesthetics were administered; b: Subgroups according to the different generation of lithotripsy. VAS – visual analog scale.

First, 2 subgroups were established according to whether IV anesthetics were administered at the start of the operation. Patients in subgroup 1 received IV anesthetics only when needed, and patients in subgroup 2 received IV anesthetics in combination with EMLA during the entire ESWL procedure. Heterogeneity was not reported among the studies in the pooled analysis in subgroup 1 (p=0.650, I^2=0.0%; Figure 3) and subgroup 2 (p=0.200, I^2=38.0%; Figure 3), but it was observed in all patients (subgroup 1 and subgroup 2 together) (p=0.020; I^2=62.0%; Figure 3). The division of subgroups in our meta-analysis successfully decreased the heterogeneity.

Subgroup 1 consisted of 3 trials, including 113 patients who received EMLA and 110 who received placebo. The MD of subgroup 1 was –0.15 (95% CI, –0.45 to 0.15; p=0.320), so there was no significant difference in the VAS scores between patients receiving EMLA and those receiving placebo. Subgroup 2 contained 3 trials, including 287 patients who received EMLA and 391 patients who received placebo. The MD of subgroup 2 was –0.70 (95% CI, –0.99 to –0.42; p<0.0001), which showed a significant difference in the VAS scores between the patients who received EMLA and those who received placebo.

Then, according to the different generation of lithotripsy used in different trials, we divided our result into 4 subgroups: the third-generation lithotripsy subgroup, the second-generation lithotripsy subgroup, the first-generation lithotripsy subgroup, and the generation unknown subgroup. Only 1 trial was included in each of the last 3 subgroups, so the heterogeneity was not available for each subgroup. In the third-generation lithotripsy subgroup, heterogeneity was observed (p=0.020, I^2=74.0%; Figure 3). The third-generation lithotripsy subgroup consisted of 3 trials, in which 227 patients received EMLA and 332 patients received placebo. The MD of the third-generation subgroup was –0.58 (95% CI, –1.07 to –0.10; p=0.020), which showed a significant difference between the patients who received EMLA and those who received placebo. No significant difference was observed in the other 3 groups.

Evaluation of all patients together showed that the total MD was –0.47 (95%, –0.78 to –0.16; p=0.003), which showed a significant difference between the patients who received EMLA and those who received placebo. Since the VAS score represents the severity of pain, lower VAS scores in the EMLA group mean less pain compared to the placebo group during the ESWL procedure.

Duration of ESWL

Four trials, including 244 patients, reported the mean duration of ESWL. There were 122 patients in the EMLA group and 122 patients in the placebo group. Heterogeneity among the studies was insignificant in the pooled analysis (p=0.280; I^2=23.0%; Figure 4). The total MD was –1.70 (95% CI, –2.31 to –1.10; p<0.0001), and the mean duration of ESWL was significantly shorter in the EMLA group than in the placebo group.

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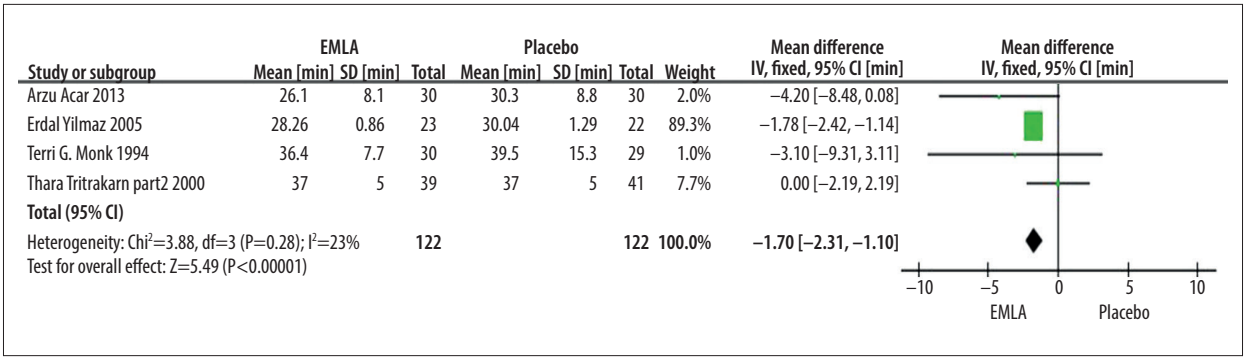

Figure 4. Forest plot analysis showing the duration of ESWL.

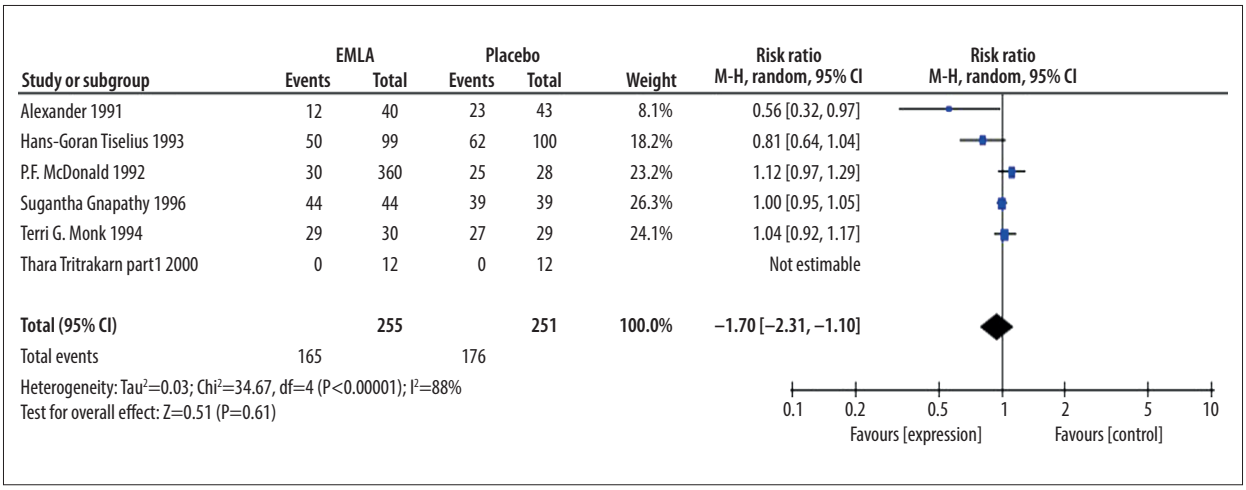

Figure 5. Forest plot analysis showing the number of patients needed extra IV medication. IV – intravenous.

EMLA *vs.* placebo for patients who needed extra IV medication

Six trials, including 506 patients, reported the number of patients who needed extra IV medication during ESWL: 255 patients in the EMLA group and 251 patients in the placebo group. Heterogeneity among studies was significant in the pooled analysis ($p<0.0001$, $I^2=88.0\%$; Figure 5). The RR was 0.95 (95% CI, 0.79 to 1.15; p=0.610), and no significant difference was found in the number of patients who needed extra IV medication between the EMLA and placebo groups.

EMLA *vs.* placebo for opioid adverse effects

Four trials, including 282 patients, reported patients with adverse effects after ESWL, including 143 patients in the EMLA group and 139 patients in the placebo group. The reported adverse effects of opioids included hypotension, respiratory depression (including SPO2 <90%, bradypnea, apnea >20 seconds), nausea, vomiting, dizziness, and pruritus. There was no heterogeneity among the studies in the pooled analysis (p=0.920; $I^2=0.00\%$; Figure 6), so the fixed model was used. The total RR was 0.86 (95% CI, 0.64 to 1.16; p=0.320), which shows that there was no significant difference in the incidence of opioid adverse effects between the EMLA group and placebo group.

Patients who experienced insufficient pain control

We included 7 trials with 447 patients treated with EMLA and 549 patients treated with placebo. There were 188 patients in the EMLA group and 215 patients in the placebo group who experienced insufficient pain control during ESWL. There was high heterogeneity among the studies in the pooled analysis ($p<0.0001$; $I^2=86.0\%$; Figure 7). The RR was 0.94 (95% CI, 0.78 to 1.14; p=0.530). There was no significant difference between the 2 groups.

Discussion

ESWL was a painful treatment when it was first introduced to clinical practice [20–22]. If not well managed, pain will cause the patient to move during the procedure, which can lead to a defocused shock wave that reduces stone fragmentation and lowers stone clearance [8,23]. Recently, a number of studies have prescribed opioids for pain control in ESWL, but adverse effects, such as bradycardia and hypotension, can occur and

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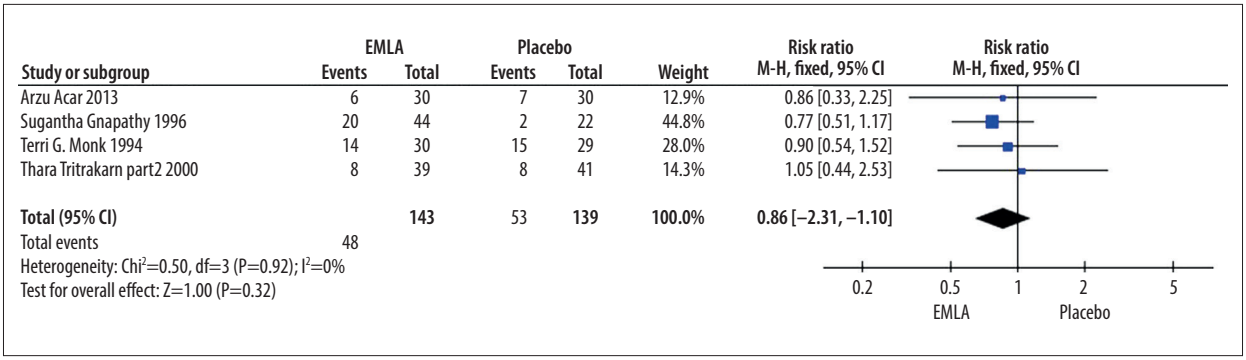

Figure 6. Forest plot analysis showing the number of patients showing adverse effects of opioids.

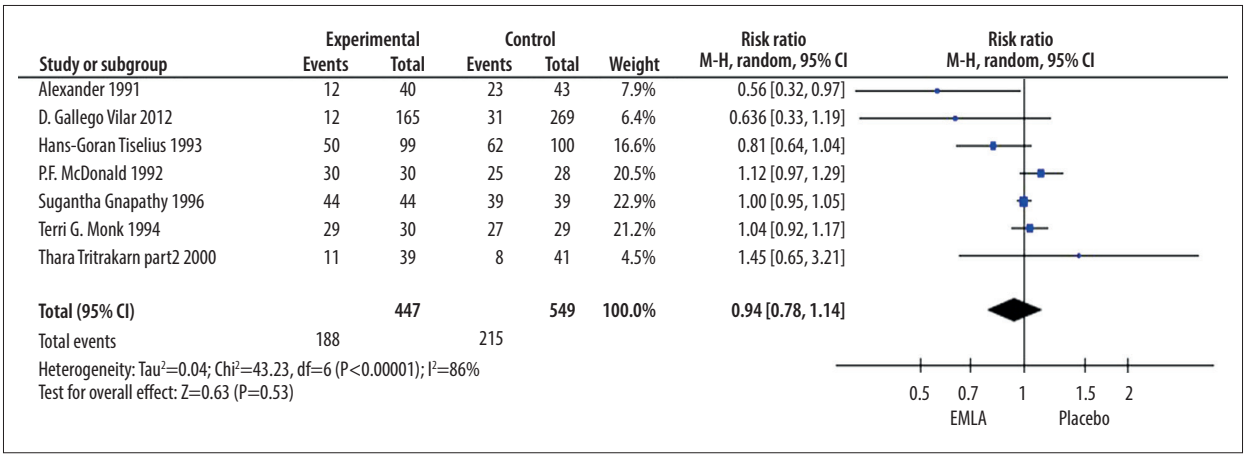

Figure 7. Forest plot analysis showing the numbers of patients felt insufficient pain control during the ESWL procedure.

lead to serious consequences [5,24–26]. The requirement for electrocardiography and blood pressure and oxygen saturation monitoring makes the process inconvenient [27]. NSAIDs are usually given intravenously and intramuscularly. However, NSAIDs are contraindicated for patients with renal impairment [28], which is common in patients with urinary stones, and caution is needed when administering NSAIDs to patients with conditions such as hepatic insufficiency, chronic obstructive pulmonary disease, histories of heart failure, and hypertension [29]. In addition, as gross hematuria is a common complication of ESWL, the effect of NSAIDs on coagulation may worsen this complication [30]. Intracutaneous sterile water injection (ISWI) has been used for relief of low back pain. ISWI can relieve pain effectively, and it can improve movement in patients with acute low back pain during labor [31]. The possible mechanisms of ISWI include a gate control mechanism and diffuse noxious inhibitory control [32,33]. Studies have focused on the application of ISWI to ESWL, which demonstrated that ISWI is safe, simple, and effective for pain relief [9]. However, ISWI requires patients to endure temporary intradermal injection, which can cause severe pain, and there are few relevant studies on use in ESWL. Existing studies suggest that the result of ISWI in the ESWL procedure are uncertain, and more evidence is needed to confirm the effectiveness of this therapy.

Topical application of dermal anesthesia, such as EMLA, is also an alternative [8]. Dermal anesthetics have advantages in that complications are rarely observed with proper application [11], and the treatment is simple and noninvasive, with few contraindications [34]. According to a review article, 9 pediatric patients and 3 adult patients with systemic toxicity due to EMLA have been reported from 1985 to 2013 [11]. Further, in 1 RCT, the reported effect of EMLA on pain control in ESWL was the same as the effects of opioids and NSAIDs [35]. However, conflicting results were found concerning the efficacy of EMLA for pain relief during ESWL in our meta-analysis [5,17,35,36].

In our meta-analysis, we found that the VAS scores were significantly lower in the EMLA group than in the placebo group during the ESWL procedure for all patients and in the subgroup of patients using EMLA in combination with IV anesthetics during the entire ESWL procedure. However, for patients treated with IV anesthetics only when needed, there was no obvious difference between the EMLA group and placebo group. The lower VAS scores in the EMLA group suggested that EMLA does reduce pain during ESWL when accompanied by IV anesthesia, but the analgesic effect was not as strong for EMLA used alone. This result proves that EMLA counteracts the cutaneous component of the pain better than the visceral component during

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ESWL [5]. Because ESWL procedure can induce pain via the direct action of shock waves on cutaneous nociceptors, as well as increased intrapelvic pressure on visceral nociceptors, with other IV analgesics/anesthetics on board to achieve abirritation through visceral nociceptors, the effect of EMLA on cutaneous pain will no longer be concealed. Consistent with this, compared to the minor and insignificant reduction of VAS score for patients treated with IV anesthetics only when needed, the subgroup of patients using EMLA in combination with IV anesthetics during the entire ESWL procedure had a reduction of up to 0.95 (p=0.000) on the scale from 0 to 10 in the VAS. This is clinically significant, because in the included studies, patients typically had average VAS scores near or above 4 (moderate pain) with placebo during ESWL (data not shown), and with a reduction of 0.95, the score could be less than 3, which could be considered mild enough [37]. We also found that EMLA can significantly decrease the VAS score in the third-generation lithotripsy subgroup, and the effect of pain control is relatively low when applied with the older generations of lithotripsy. With the development of technology, more advanced lithotripsy causes less pain in the ESWL procedure. Because the older generations of lithotripsy are not commonly used, EMLA could be a good choice for pain control in the ESWL procedure.

The duration of ESWL was significantly shorter in the EMLA group than in the placebo group. Uncontrolled pain during the process increases patient movement and the shockwaves could be out of focus, resulting in longer duration, while a shorter duration demonstrates the opposite. Although shortening the ESWL procedure by 2 minutes during by use of EMLA may not be clinically significant, it shows that less pain was experienced after applying EMLA.

Most trials have used opioids in PCA devices or as IV medications for supplementary anesthesia, so we tried to assess the effect of EMLA by comparing the amount of opioids consumed, but we failed because different kinds of opioids were prescribed and various ways of counting IV medication consumption were used in the different studies. Instead, we analyzed the number of patients who needing extra IV medication and the number of patients who complained of insufficient pain control, and no significant difference was found between these groups, which indicated that EMLA cream was not strong enough to reduce opioid consumption. The similar incidences of opioid adverse effects in the EMLA group and placebo group also indirectly proved this point.

Pain relief from treatment with EMLA in the ESWL procedure may be explained as follows except for the local anesthetic effect [38]: EMLA can function as a coupling medium, which reduces acoustic impedance when applied to skin, less reflection and absorption of energy occurs at the skin–cream interface, and thus pain is alleviated when shock waves are administered [15]. Furthermore, because the cavitation effect of shock waves induces tissue damage, EMLA, which is a viscous fluid, can inhibit development of cavitation and reduce pain during ESWL [39,40].

One study that compared the analgesic effect of oral diclofenac alone, EMLA alone, or a combination of these 2 drugs showed that the combination group achieved the best result [36]. The researchers found that the combination of EMLA and diclofenac could increase the stone-free rate with fewer complications or need for additional anesthesia. However, no other studies have evaluated the analgesic effect of the combination of EMLA and other drugs. Further studies for evaluation of the effect of the combination of EMLA and other drugs on pain relief are warranted.

For more than 30 years, pain during the ESWL procedure has been an unsolved problem. Despite the relatively weak effect of EMLA on pain control, researches still regard EMLA as a good analgetic for use during the ESWL procedure because of its simple application method and good safety. EMLA is easy to apply to skin and does not require monitoring of vital signs. Regarding safety, unlike opioids and NSAIDs, which need to be consumed or injected, EMLA is applied cutaneously and is thus much safer. Our research showed EMLA could decrease the VAS score in ESWL, and recent studies in which ESWL was performed using third-generation lithotripsy have shown a more effective pain-relieving outcome by using EMLA than in earlier studies. For all of these reasons, use of EMLA is beneficial during ESWL. Our results suggest that, for patients without severe pain during the ESWL procedure but who still need pain control, EMLA is beneficial during ESWL, particularly when considering the adverse effects and extra IV procedure of opioids and NSAIDs.

Limitations

The main limitation of this study was the >20-year interval between the earliest article and the latest one, and during this period, different kinds of lithotripters, energy magnitudes, and numbers of shockwaves in ESWL have been used in the various studies. Among them, different generations of lithotripters were considered to be a key factor that may influence the results, so we did a subgroup analysis according to the different generations of lithotripsy, but we still detected no significant differences. The studies included in our analysis used different doses of EMLA applied to different sizes of skin areas, which may account for the higher heterogeneity observed. Under this condition, random-effects models were used to erase the impact of high heterogeneity on the results. Furthermore, the studies did not report enough data on the stone-free rate, so we could not analyze it. Additionally, the VAS score was our primary outcome, but this is a subjective scale that may have a relatively high risk of bias, but it is still considered the criterion standard for pain assessment. Since there were only 9 papers included in our meta-analysis, we did not evaluate publication bias.

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Conclusions

EMLA can reduce pain during the ESWL procedure, and the effect of pain control is better when combined with other drugs or when third-generation lithotripsy is used. EMLA can also reduce the time required for the ESWL procedure. We recommend EMLA be used for patients without severe pain during the ESWL procedure but who still need pain control, and for those with contraindications of opioids and NSAIDs.

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