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ORIGINAL ARTICLE

# Efficacy and safety of local anaesthetics for premature ejaculation: a systematic review and meta-analysis

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**To assess the efficacy and safety of local anaesthetics for premature ejaculation (PE), a systematic review of the literature was performed using the Cochrane Library, PUBMED and EMBASE. We screened and retrieved the randomized controlled trials on the treatment of PE with local anaesthetics. End points included intravaginal ejaculation latency time (IELT), patient-reported outcome assessments and adverse events. Meta-analyses were conducted with Stata 11.0. In total, seven publications involving 566 patients with local anaesthetics and 388 with placebos strictly met our eligibility criteria. Meta-analyses showed that after the patients were treated with the local anaesthetics, the value of the standardized mean difference of the changes in IELT was 5.02 (95% CI: 3.03–7.00). A higher rate of adverse events occurred compared with placebos (odds ratio: 3.30, 95% CI: 1.71–6.36), but these events were restricted to local side effects. In addition, significantly greater improvement was observed in patient-reported outcomes. In summary, local anaesthetics can prolong IELT and improve ejaculatory control and sexual satisfaction.**
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**Keywords:** local anaesthetics; premature ejaculation (PE); randomized controlled trial; systematic review

## INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction and affects 20%–30% of the world's male population.[1] PE may cause mental distress, anxiety, embarrassment and depression; therefore, it negatively affects one's self-confidence and the relationship with one's spouse. There are multiple definitions of PE. In 2008, lifelong PE was defined as 'a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within approximately 1 min of vaginal penetration; the inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy' by the International Society of Sexual Medicine (ISSM).[2] This constitutes the first contemporary multivariate evidence-based definition. Unfortunately, many patients complaining of PE do not meet these criteria; however, these cases may be diagnosed as a subtype of PE, namely, acquired PE, nature-variable PE or premature-like ejaculatory dysfunction.[3]

Previously, it was thought that the aetiology of PE was psychological and based on certain conditioning factors, including unresolved unconscious conflicts, interpersonal problems, inappropriate conditioning by early experiences and a too low frequency of sex.[4] Over the past two decades, some studies have implied that PE may be caused by somatic disorders and/or neurobiological disturbances.[5–8] Recently, ISSM promulgated an evidenced-based, comprehensive and practical set of clinical guidelines for the treatment of PE.[9] They indicated that treatment options for men with PE were largely based on selective serotonin reuptake inhibitors (SSRIs) and on-demand topical anaesthetic agents, which were supported by level 1a and 1b evidence, respectively. At the same time, other treatments were not recommended due to the lack of high-quality evidence. To date, no pharmacological agents have been approved for use in PE, apart from dapoxetine in some European countries.[10]

Many studies have investigated the therapeutic role of topical anaesthetic agents in PE. However, in this era of evidence-based medicine, an important consideration is the availability of adequate supportive clinical data. Therefore, we applied systematic evaluation and meta-analysis of the available data regarding the use of topical anaesthetic agents to treat patients with PE while focusing on adverse-events profiles.

## MATERIALS AND METHODS

### Publication search

We performed a systematic review of the literature by electronically searching the Cochrane Library, PUBMED and EMBASE up to October 2012. The search terms included the keywords 'anaesthetics', 'premature ejaculation', 'SS-cream', 'PSD502', 'lidocaine', 'prilocaine' and 'TEMPE' (alone and in combination). All of the references in the relevant articles were screened for any further articles that were not identified in the initial search. Two reviewers independently searched and extracted the data according to the defined inclusion and exclusion criteria.

### Inclusion and exclusion criteria

Inclusion criteria were as follows: (i) comparison of local anaesthetics to a placebo for PE, with quantitative data on outcome parameters; (ii) specification of the criteria for the diagnosis of lifelong PE; and

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(iii) measurement of intravaginal ejaculatory latency time (IELT) during the intercourse event. Exclusion criteria were as follows: (i) incomplete data availability; (ii) duplicated or updated data; (iii) non-inclusion of their own data, such as reviews, comments, editorials, letters and congress; and (iv) case reports.

### Data extraction

Two blinded reviewers (JDX and YFH) independently extracted and recorded the following information: first author's surname, year of publication, type of design, drug dosage and time, number of participants, type of ejaculation syndrome treated, definition of PE, main study end points and side events. Of the seven included studies, two provided geometric means, medians and ranges instead of means and standard deviation,[20,21] and their sample sizes were both greater than 70. As Hozo *et al.*'s[11] methodology is suitable in either normally or non-normally distributed data, we used this methodology to estimate the mean and standard deviation from the median, range and the size of a sample for large samples. Briefly, the median can be used to estimate mean; the formula range/6 was the estimator for the standard deviation. Disagreements were resolved through consensus with a third reviewer (LHZ).

### Quality assessment of included studies

Two independent reviewers (JDX and YFH) systematically performed the methodological quality assessment of selected studies according to the Jadad scale.[12] The quality criteria assessed were as follows: generation of an allocation sequence, investigator blindness and description of withdrawals and dropouts. Disagreements were discussed by the reviewers and resolved through consensus. Total scores ranged from 0 to 5. We defined scores between 3 and 5 as being high quality, with those less than three as being low quality.

### Statistical analysis

Meta-analyses were performed for IELT and adverse events outcome parameters. The chi-squared test and inconsistency index (*I*-squared, $I^2$) were used to estimate the heterogeneity.[13] The chi-squared test assessed whether observer differences in results were compatible with chance alone. A $P<0.1$ indicated the presence of heterogeneity. An $I^2$ index was calculated to describe the percentage of the variability that is from heterogeneity rather than chance. $I^2>50\%$ was considered to be significant for heterogeneity. When heterogeneity was not significant, the fixed-effects model of Mantel–Haenszel was used to obtain summary statistics for the overall differences in IELT.[14] Otherwise, the random-effect model weighted by DerSimonian–Laird was selected.[15] In situations with substantial heterogeneity, the subgroup analysis and meta-regression analysis were used to explore the sources of heterogeneity based on the characteristics of the studies, and a sensitivity analysis was conducted to assess the stability of the results. Namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the overall effect. We calculated the standardized mean difference (SMD, at 95% confidence intervals (CI)) to standardize the outcome of each individual study by the size of the effect in terms of the observed standard deviation. The SMD is also known as Cohn's effect size, which is useful in meta-analyses because it eliminates the problem of units of measurement and duration.[16] If the value 0 is not within the 95% CI, then the SMD is statistically significant at the 5% level ($P<0.05$). Cohen's rule of thumb for the interpretation of the SMD statistic is as follows: a value of 0.2 indicates a small effect; a value of 0.5, a medium effect; and a value of 0.8 or larger, a large effect.[17] Pooled odds ratios (at 95% CI) were calculated to analyse adverse events. Statistical analysis was performed using Stata version 11.0 (Stata Corporation, College Station, TX, USA).

## RESULTS

### Characteristics of the included studies

A total of 75 studies were initially identified using the search strategy. However, after screening the titles and abstracts, 61 studies were excluded. Of the 14 remaining studies, seven published articles were ultimately identified as meeting the inclusion and exclusion criteria (**Figure 1**).

The study characteristics and methodology for the seven studies are shown in **Table 1**. Of these studies, four were doubled-blind, placebo-controlled, randomized trials (three multicentre studies);[18–21] two were *N*-of-1 randomized, double-blind, placebo-controlled trials (one multicentre study);[22,23] and the last one was a prospective, randomized, single-blind, placebo-controlled study.[24] In short, all included studies were randomized, placebo-controlled trials (RCTs). Lifelong PE was the main inclusion parameter, and three studies also enrolled patients with secondary PE.[18,20,21] The definitions of PE in these studies were very different. IELT was measured using a stopwatch to define PE in all but one study.[24] All included studies were of adequate quality (Jadad scores $\geqslant 3$).

### Efficacy evaluation

*Influences on IELT.* IELT is defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation and acts as a leading factor for the assessment of clinical effectiveness in treating PE.[25] All of the studies reported IELT changes before and after treatment with the local anaesthetics. No differences in the pre-treatment IELT were found between the treatment and control groups (**Table 2**); thus, post-treatment IELT was the most important point for assessing efficacy. Choi *et al.*[22] investigated the efficacy of SS-cream at various doses and found that 0.2 g was the clinically optimal dose; we chose the 0.2 g as the base dose for our analysis. Similarly, the efficacy of an eutectic mixture of local anaesthetics (EMLA) cream was evaluated by Atikeler *et al.*[24] at different usage times, and the results indicated that 20 min was the optimal period. A 20-min usage time was considered as the baseline for the analysis. In total, the trials comprised 566 patients using local anaesthetics and 388 using placebos. The random-effect model SMD was 5.02 (95% CI: 3.03–7.00; $P<0.001$ for the heterogeneity), suggesting that the effect of local anaesthetics is statistically superior to that of a placebo for a prolonged time in IELT in treating PE, regardless of any differences in drugs and forms (**Table 2** and **Figure 2**).

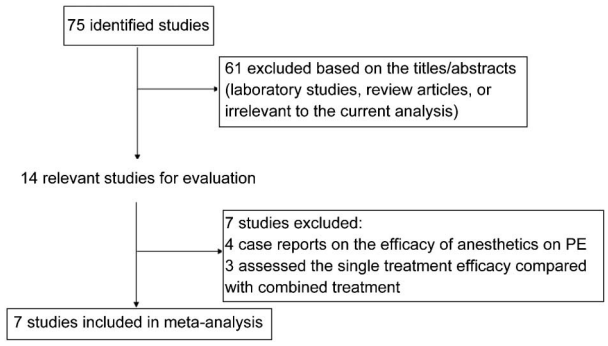


**Figure 1** Flow diagram of the studies identified in the meta-analysis.

**Table 1 Methodology of the included studies**

| *Author* | *Year* | *Design* | *Drug dosage and time* | *Subjects* (n) | *Ejaculation syndromes* | *PE definition* | *Main study end points* | *Jadad score* |
|---|---|---|---|---|---|---|---|---|
| Choi *et al.*[23] | 2000 | *N*-of-1 randomized double-blind placebo-controlled | SS-cream (0.2 g,1 h) | 106 | Lifelong | IELT <3 min, SSR <30% in both patients and partners | Stopwatch IELT, SSR | 4 |
| | | | Placebo | 106 | | | | |
| Choi *et al.*[22] | 1999 | *N*-of-1 randomized double-blind placebo-controlled | SS-cream (0.05 g, 1 h) | 50 | Lifelong | IELT <3 min, SSR <30% in both patients and partners | Stopwatch IELT, SSR | 4 |
| | | | SS-cream (0.10 g, 1 h) | 50 | | | | |
| | | | SS-cream (0.15 g, 1 h) | 50 | | | | |
| | | | SS-cream (0.20 g, 1 h) | 50 | | | | |
| | | | Placebo | 50 | | | | |
| Atikeler *et al.*[24] | 2002 | Randomized, single-blind, placebo-controlled | EMLA (2.5 g, 20 min) | 10 | Lifelong | IELT <1 min | IELT | 3 |
| | | | EMLA (2.5 g, 30 min) | 10 | | | | |
| | | | EMLA (2.5 g, 45 min) | 10 | | | | |
| | | | Placebo | 10 | | | | |
| Dinsmore *et al.*[19] | 2007 | Randomized, doubled-blind, placebo-controlled | TEMPE (7.5 mg lidocaine and 2.5 mg prilocaine, 15 min) | 26 | Lifelong | DSM-IV | Stopwatch IELT, index of ejaculatory control and SQoL scores | 4 |
| | | | Placebo | 28 | | | | |
| Busato *et al.*[18] | 2004 | Randomized, doubled-blind, placebo-controlled | EMLA (2.5 g, 10 min–20 min) | 16 | Lifelong, acquired | DSM-IV | Stopwatch IELT, sexual satisfaction | 4 |
| | | | Placebo | 13 | | | | |
| Dinsmore *et al.*[20] | 2009 | Randomized, doubled-blind, placebo-controlled | PSD502 (three actuations[a], 5 min) | 191 | Lifelong, acquired | DSM-IV and ISSM | Stopwatch IELT, IPE and PEP | 4 |
| | | | Placebo | 99 | | | | |
| Carson *et al.*[21] | 2010 | Randomized, doubled-blind, placebo-controlled | PSD502 (three actuations, 5 min) | 167 | Lifelong, acquired | DSM-IV and ISSM | Stopwatch IELT, IPE and PEP | 4 |
| | | | Placebo | 82 | | | | |

Abbreviations: DSM-IV, The Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EMLA, eutectic mixture of local anaesthetics cream; IELT, intravaginal ejaculation latency time; IPE, Index of Premature Ejaculation; ISSM, International Society of Sexual Medicine; PEP, Premature Ejaculation Profile; PSD502, also known as TEMPE; SQoL, sexual quality of life; SS-cream, extracts of nine natural products; SSR, sexual satisfaction ratio; TEMPE, topical eutectic mixture for premature ejaculation.
[a] PSD502 metered-dose spray contains 7.5 mg lidocaine and 2.5 mg prilocaine in each actuation.

However, our pooled estimates for these studies had significant heterogeneity. For example, IELT was presented as an arithmetical mean in five studies[18,19,22–24] and as a geometrical mean in the remaining two studies;[20,21] three different drugs were used in the seven studies. To address whether this heterogeneity was caused by differences in types of drug, study design (*N*-of-1 RCTs or non-*N*-of-1 RCTs), or IELT expressions, we performed the meta-regression. The results demonstrated that the types of drugs and study designs could account for the substantial heterogeneity ($P$=0.002 and 0.032, respectively), while the IELT expressions were not associated with the heterogeneity

**Table 2 Outcomes of the included studies**

| *Author* | *Treatment* | *Pre IELT (min)* | *Post IELT (min)* | *Adverse events* (n) |
|---|---|---|---|---|
| Choi *et al.*[23] | SS-cream | 1.37±0.12 | 10.92±0.95 | 10 |
| | Placebo | 1.37±0.12 | 2.45±0.29 | 4 |
| Choi *et al.*[22] | SS-cream[a] | 1.35±0.07 | 11.06±1.17 | 12 |
| | Placebo | 1.35±0.07 | 2.27±0.32 | Not reported |
| Atikeler *et al.*[24] | EMLA[b] | 1.00 | 6.71±2.54 | Not reported |
| | Placebo | 1.00 | 1.01±0.07 | Not reported |
| Dinsmore *et al.*[19] | TEMPE | 1.0±1.2 | 4.9±4.9 | 6 |
| | Placebo | 0.9±0.7 | 1.6±1.6 | 4 |
| Busato *et al.*[18] | EMLA | 1.49±0.9 | 8.45±0.9 | 5 |
| | Placebo | 1.67±0.7 | 1.95±0.12 | 0 |
| Dinsmore *et al.*[20] | PSD502 | 0.6±0.38 | 3.8±9.58 | 18 |
| | Placebo | 0.6±0.55 | 1.1±2.5 | 3 |
| Carson *et al.*[21] | PSD502 | 0.56±0.22 | 2.6±6.73 | 17 |
| | Placebo | 0.53±0.25 | 0.80+1.3 | 1 |

Abbreviations: EMLA, eutectic mixture of local anaesthetics cream; PSD502, also known as TEMPE; SS-cream, extracts of nine natural products; TEMPE, topical eutectic mixture for premature ejaculation.
[a] The clinically optimal dose (0.2 g) was given.
[b] The optimal period (20 min) was given.

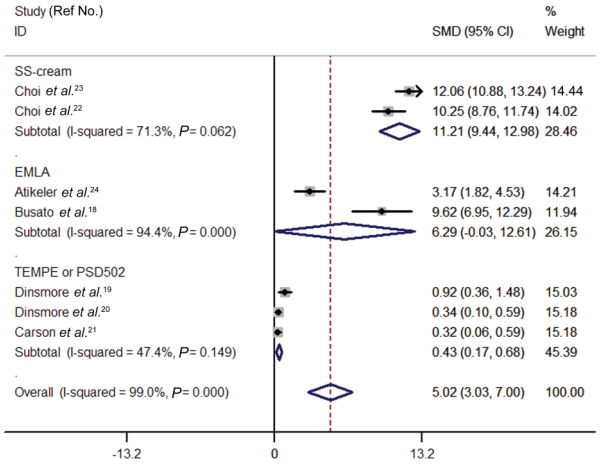


**Figure 2** Pooled estimates of the IELT of local anaesthetics *vs.* placebo. Each subgroup analysis is presented separately. Weights are from random effects analysis. EMLA, eutectic mixture of local anaesthetics; IELT, intravaginal ejaculation latency time; SMD, standardized mean difference; TEMPE, topical eutectic mixture for premature ejaculation.

($P$=0.120). As the heterogeneity was remarkable, we also conducted a sensitivity analysis with any single study omitted. The results showed that the pooled positive SMDs and 95% CI changed very little, which indicated that the meta-analysis results were stable (**Figure 3**). Publication bias was reduced to the minimum according to our search strategy. We carefully included all data into our analysis, and the baseline was maintained consistently.

### Patient-reported outcome measures

IELT is an objective measure of ejaculatory function, but cannot estimate the impact of therapy on the patients' well-being and confidence in their sexual performance, which are important markers of treatment benefit. Thus, patient-reported outcome questionnaires are used to evaluate the efficacy of the treatment. However, the rating systems and measurement characteristics in the included studies were different, and one of the reports did not present the relevant results,[24] which made it unsuitable for inclusion in the meta-analysis. Based on the International Index of Erectile Function,[26] Busato *et al.*[18] reported that scores of baseline mean intercourse satisfaction domain values were increased from 4 to 8.7 after a 2-month treatment with EMLA cream, while the scores rose from 3 to 4 in the placebo group; the difference was statistically significant ($P$<0.001). Choi *et al.*[22,23] observed that SS-cream greatly improved sexual satisfaction compared with placebo. One of the reports demonstrated that the topical eutectic mixture for premature ejaculation (TEMPE) ameliorated ejaculatory control and sexual quality of life.[19] The remaining two trials concluded that PSD502 (also known as TEMPE) was effective in treating PE according to the scores of the Index of PE and PE Profile,[27,28] which consist of questions related not only to the man's satisfaction in sexual intercourse, control over ejaculation, ejaculation-related distress and interpersonal difficulty, but also to the female partner's satisfaction.[20,21]

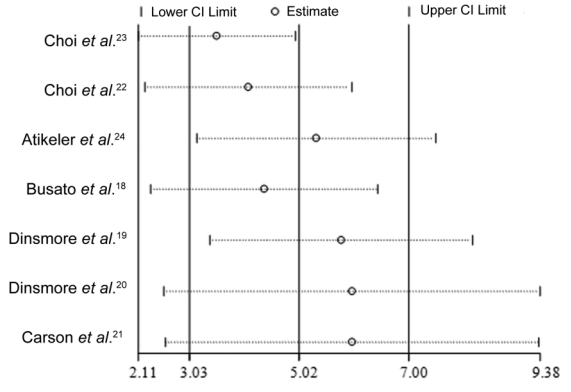


**Figure 3** The sensitivity analysis diagram for each study used to calculate the efficacy of the local anaesthetics in the treatment of PE. The given named-study is omitted.

### Safety

One trial did not mention any adverse events in either treatment or placebo group.[24] Another trial only described the adverse events in the treatment group but not in the placebo group.[23] Eventually, we incorporated the five remaining studies, which all provided the patient-reported adverse events in both groups, into the meta-analysis for the safety of local anaesthetics in treating PE. The fixed-effect model combined odds ratios was 3.30 (95% CI: 1.71–6.36, $P$=0.649 for the heterogeneity), suggesting that the topical anaesthetics had a higher adverse reaction rate (**Table 2** and **Figure 4**). The common symptoms of the patient-reported adverse events were the local side effects, such as local burning sensations, genital erythema and penile numbness, which may lead in turn to a loss of the erection. No systemic adverse events were reported in these studies.

## DISCUSSION

Based on systematic and meta-analysis, Waldinger *et al.*[29] demonstrated that the design and methodology of studies could affect the efficacy outcome differently. In this meta-analysis of seven interventional studies, all studies were randomized, prospective clinical trials with a stopwatch, and all but one were double-blind. With the high quality of these trials, we demonstrated that the s.m.d. of delaying IELT after the local anaesthetics treatment is 5.02 (95% CI: 3.03–7.00), corresponding to a significantly beneficial effect compared with placebo, although there was significant heterogeneity across the studies. Using the meta-regression analyses, we found that this heterogeneity may be caused by different types of local anaesthetic agents and study designs. Furthermore, the leave-one-out sensitivity analysis showed that the results of the meta-analysis were stable. In addition, the local anaesthetics played a significant positive improvement role in the patient-reported outcome (sexual satisfaction) of both partners. In other words, topical anaesthetic agents can have a positive effect on relationships for PE patients. With respect to side effects, it is worth noting that local anaesthetics had a higher adverse reaction rate than the placebo; however, the adverse events were generally mild, infrequent, localized and transient.

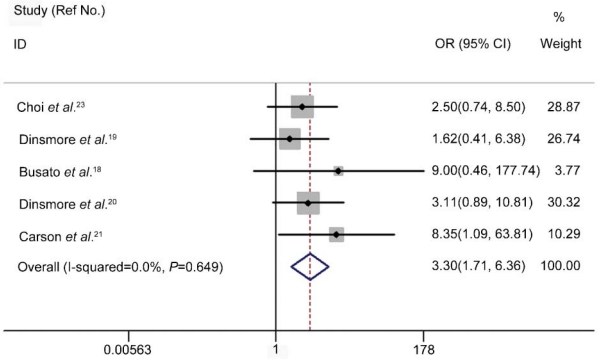


**Figure 4** Pooled estimates of side effects of the local anaesthetics *vs.* placebo.

Chronic daily treatment with oral SSRIs and other antidepressants is known to be effective in extending the IELT to treat PE.[30,31] However, daily use of SSRIs is associated with serious systemic side effects, such as nausea, diarrhoea, insomnia and headache, leading to treatment discontinuation.[32] Dapaxetine, a short-acting SSRI, has been approved for the treatment of PE in some European countries and can be used as needed 1–3 h prior to planned sexual contact. However, this drug is also accompanied by the above-mentioned treatment-related adverse effects.[33] Comparatively, local anaesthetics have a favourable benefit–risk profile and provide a consistent, durable improvement for patients with PE.

The aetiology of PE is complicated,[34] but it is now accepted that both biological and psychological factors play a role. Some researchers have suggested that the hypersensitivity and hyperexcitability of the glans penis are the basis for the uncontrolled ejaculation.[35–37] Xin *et al.*[38] found that SS-cream could prolong the sensory conduction and reduce the glans penile hyperexcitability of the patient with PE.[38] In our systematic reviews, there were three types of the local anaesthetic agents: SS-cream (70% extract of Bufonis Veneum, 10 mg; Ginseng Radix Alba fructose, 100 mg; extract of Asiasari Radix, Carophylli Flos, Cinnamoni Cortex, 10 mg),[23] EMLA (25 mg lidocaine and 25 mg prilocaine eutectic cream)[24] and TEMPE or PSD502 (22.5 mg lidocaine and 7.5 mg prilocaine eutectic mixture).[19] These drugs can produce some degree of penile desensitisation or act within the afferent-efferent reflex, thereby delaying ejaculatory latency.[5]

Our meta-analysis has some limitations. The heterogeneity of the trials is primary among these limitations, even though we performed meta-regression analyses and found that they could reduce or explain the high heterogeneity. Moreover, the definitions of PE in the included studies were extremely variable, which may constitute another potential limitation and even influence the sources' explanation of the heterogeneity. Finally, the sample sizes were dissimilar among the studies; therefore, the statistical power of each study was very different.

To overcome the limitations discussed above, we provide the following directions for the design and report of any future RCTs. First, an evidence-based definition of PE should be implemented to ensure accurate and reproducible clinical outcomes. Second, additional trials are necessary to determine the optimal formulation, dose and time of the local anaesthetics for PE treatment.

## CONCLUSIONS

Local anaesthetics can clinically and statistically prolong IELT and improve ejaculatory control and sexual satisfaction. Local anaesthetics seem to be well tolerated by the PE patients with no systemic side effects and a low incidence of localized effects; therefore, these anaesthetics appear to offer significant advantages over alternative therapies developed for the treatment of PE.

## AUTHOR CONTRIBUTIONS

YTD and JDX conceived and designed the study. JDX, YFH, LHZ and YC collected the data. JDX and LHZ performed the statistical analysis. JDX, YC and YTD drafted and revised the manuscript. All authors read and approved the final version.

## COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

## ACKNOWLEDGMENTS

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