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# Parecoxib versus Lidocaine for Attenuation of Propofol Injection Pain: A Pilot Randomized Controlled Trial

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# Abstract

**Background:** Propofol is the most widely used intravenous induction agent, but injection pain occurs in 60–70% of patients without pretreatment. Lidocaine with venous occlusion is the established reference method for prevention. Parecoxib, an injectable COX-2 inhibitor used in multimodal analgesia, has been reported in a single placebo-controlled trial to reduce this pain, but it has not been compared directly with lidocaine.

**Objective:** To compare, in a pilot trial, the efficacy of intravenous parecoxib versus lidocaine — each combined with venous occlusion — in preventing propofol injection pain, and to estimate the sample size required for a definitive trial.

**Design:** Single-centre, double-blind, randomized controlled pilot trial.

**Population:** Thirty adults (ASA I–II) undergoing elective surgery, allocated 1:1 to two arms.

**Intervention:** Lidocaine 0.5 mg/kg (maximum 50 mg) versus parecoxib 40 mg, each with venous occlusion for 120 seconds before a fixed 50 mg propofol challenge.

**Outcomes:** Primary — incidence of injection pain. Secondary — pain severity (numerical rating scale, NRS).

**Results:** Injection pain was more frequent with parecoxib (66.7%) than with lidocaine (13.3%) ($\chi^2(1) = 8.889$, $p = 0.003$; absolute risk reduction 53.4%; relative risk 5.0) Pain severity was also greater with parecoxib (median NRS 2, IQR 0–5) than with lidocaine (median NRS 0, IQR 0–0) (Mann–Whitney $U = 48.5$, $p = 0.007$).

**Conclusion:** In this pilot, parecoxib with venous occlusion did not reduce propofol injection pain relative to lidocaine, and its performance was comparable to historical untreated rates. These preliminary findings support lidocaine with venous occlusion as the more effective pretreatment and warrant confirmation in a larger, adequately powered multicentre trial.

**Trial registration:**

ClinicalTrials.gov NCT07116304 (https://clinicaltrials.gov/study/NCT07116304).

Trial registration date: 31 July 2025, before enrolment of the first participant.


# Introduction

Propofol is the most commonly used agent for induction of anaesthesia because of its rapid onset, wide availability, and predictable, well-characterised pharmacological profile. A recognised drawback is pain on injection: without pretreatment, 60–70% of patients experience it, with varying severity [1]. The mechanism is incompletely understood but is thought to involve activation of the kallikrein–kinin

cascade at the injection site [2]. Numerous strategies have been evaluated to reduce both the incidence and severity of this pain. Pretreatment with lidocaine combined with venous occlusion is consistently identified as the most effective single measure, reducing incidence by up to 80% [1, 3].

Parecoxib is an injectable, selective COX-2 inhibitor and a prodrug that is converted to the active metabolite valdecoxib [4]. It is widely used within multimodal analgesic regimens for postoperative pain and opioid sparing. A single randomized, placebo-controlled trial reported that parecoxib pretreatment with venous occlusion reduced propofol injection pain in both incidence and severity [5]. However, parecoxib has never been compared directly against lidocaine, the reference standard, for this indication.

We designed this pilot trial to compare pretreatment with lidocaine versus parecoxib, each with venous occlusion, for preventing propofol injection pain, and to generate the effect-size estimates needed to power a definitive trial. Because parecoxib's established value in multimodal analgesia is distinct from the mechanism of acute injection pain, we regarded the comparison as exploratory rather than assuming equivalence.

## Methods

# Study design

This was a prospective, single-centre, double-blind, randomized controlled pilot trial conducted at the Medical City Hospital for Military and Security Services (MCMSS), Oman. Ethical approval was granted by the institutional Medical Research Ethics Committee (approval date 22 July 2025), and the trial was prospectively registered on ClinicalTrials.gov (NCT07116304) before enrolment of the first participant. Reporting follows the CONSORT 2025 statement and the CONSORT extension for randomized pilot and feasibility trials. Participants were recruited between August 2025 and October 2025. Patients and members of the public were not involved in the design, conduct, reporting, or dissemination planning of this study. No important changes were made to the trial protocol after commencement of the study.

## Participants

Adults older than 18 years, ASA physical status I–II, scheduled for elective surgery were eligible. Exclusion criteria were: age under 18; known allergy to propofol, NSAIDs, or lidocaine; pregnancy; ASA III–VI; chronic kidney disease or hepatic impairment; known gastrointestinal bleeding; asthma; and receipt of any analgesic within the preceding hour. Written informed consent was obtained from every participant, using Arabic or English consent forms.

## Randomization, allocation concealment, and blinding

Participants were randomized 1:1 using a computer-generated block sequence; the block size was withheld from the investigators to preserve allocation concealment. Allocation was concealed using

sequentially numbered, opaque, sealed envelopes, opened only at the point of drug preparation. Personnel responsible for participant enrolment did not have access to the random allocation sequence before assignment. The study drug was prepared by an anesthesia nurse who was not otherwise involved in patient assessment, and was presented as a 5 mL transparent solution labelled “study drug.” Both the patient and the attending anaesthetist were blinded to allocation, as was the outcome assessor, who was a separate person from the anaesthetist delivering induction.

## Intervention

Participants received either parecoxib 40 mg (Group P) or lidocaine 0.5 mg/kg to a maximum of 50 mg (Group L), each diluted to 5 mL with 0.9% saline to yield a visually identical transparent solution.

After application of standard ASA monitoring (ECG, non-invasive blood pressure, pulse oximetry), a 20-gauge cannula was inserted into the dorsum of the hand and flushed to confirm patency. Venous occlusion was produced using the anaesthesia machine’s non-invasive blood pressure cuff inflated to 80 mmHg; the cuff was inflated immediately before administration of the study drug and maintained for 120 seconds. A fixed challenge of 50 mg propofol (1% medium-/long-chain triglyceride emulsion, Fresenius Kabi) was then administered over 5 seconds, with the propofol at room temperature (operating-theatre ambient temperature approximately 20°C).

Immediately after the propofol challenge, the blinded assessor asked the patient about pain if it had not been reported spontaneously, and recorded severity on a 0–10 NRS. The injection site was inspected for local reactions (wheals or erythema). Thereafter, routine induction proceeded (fentanyl, the remaining 1–2 mg/kg of propofol, and any other agents chosen by the attending anaesthetist). No analgesic other than the study drug was given before pain assessment, to avoid confounding.

## Outcomes

The primary outcome was the incidence of pain on propofol injection. The secondary outcome was pain severity, scored on a 0–10 NRS where pain occurred.

# Statistical analysis

As a pilot, the primary analytic purpose was to estimate the effect size and its variability in order to power a definitive trial; formal hypothesis testing is presented as exploratory and interpreted with caution.

The incidence of pain was compared using the Pearson chi-square test; all expected cell counts were ≥ 5 (minimum expected count 6.0), so the test’s assumptions were satisfied. The treatment effect on incidence is reported as the absolute risk difference and relative risk, each with a 95% confidence interval, and as the number needed to treat. NRS scores, being ordinal and non-normally distributed, are

summarised as median (interquartile range) and compared using the Mann–Whitney U test; the effect size is reported as the rank-biserial correlation. Baseline characteristics are described descriptively without significance testing, consistent with CONSORT guidance. A two-sided α of 0.05 was used. Analyses were performed using IBM SPSS Statistics. There were no missing outcome data; all randomized participants were included in the analysis. No subgroup, sensitivity, or other ancillary analyses were performed.

## Sample size estimation

Because no previous study had directly compared these two agents, no reliable head-to-head effect estimate was available for a conventional a priori sample-size calculation; the trial was therefore designed as a pilot study to estimate the treatment effect and to determine the sample size required for a confirmatory trial. Based on the incidence observed in this pilot (66.7% vs 13.3%) and a two-sided α of 0.05, a post-hoc calculation suggested that approximately 14 participants per arm would be required to detect a difference of this magnitude. However, because this estimate was derived from the same small pilot cohort, it should be interpreted cautiously, as pilot studies may overestimate treatment effects. The findings are therefore considered preliminary and would benefit from confirmation in a larger, adequately powered multicentre trial. No interim analyses were planned or performed, and no formal stopping guidelines were specified.

## Results

Thirty patients were randomized (15 per arm); none were excluded or withdrawn after randomization, and all 30 were analysed. Baseline characteristics were comparable between groups (Table 1). Outcome assessment was completed immediately after the propofol challenge, with no additional follow-up required.

Table 1
Baseline characteristics of study participants.

| Characteristic | Lidocaine (n = 15) | Parecoxib (n = 15) |
|---|---|---|
| Age, mean ± SD (years) | 35 ± 10 | 36 ± 11 |
| Sex (M/F) | 8/7 | 9/6 |
| Weight, mean ± SD (kg) | 72 ± 12 | 74 ± 13 |
| ASA I/II | 10/5 | 9/6 |

The incidence of injection pain was higher in the parecoxib group (66.7%, 10/15) than in the lidocaine group (13.3%, 2/15) ($\chi^2(1) = 8.889$, $p = 0.003$). The absolute risk reduction was 53.4% (95% CI approximately 24% to 83%), the relative risk of pain with parecoxib was 5.0 (95% CI approximately 1.3 to

19), and the number needed to treat with lidocaine rather than parecoxib to prevent one episode of pain was approximately 2 (Table 2).

Table 2
Incidence and severity of propofol injection pain.

| Outcome | Lidocaine (n = 15) | Parecoxib (n = 15) | Effect estimate | p-value |
|---|---|---|---|---|
| Incidence of pain, n (%) | 2 (13.3%) | 10 (66.7%) | ARR 53.4% (95% CI ~ 24–83%); RR 5.0 (~ 1.3–19); NNT ≈ 2 | 0.003 ($\chi^2$) |
| NRS severity, median (IQR) | 0 (0–0) | 2 (0–5) | Rank-biserial ≈ 0.57 | 0.007 (Mann–Whitney) |
| NRS severity, mean ± SD | 0.40 ± 1.06 | 2.87 ± 2.64 | — | — |

| Outcome | Lidocaine (n = 15) | Parecoxib (n = 15) | Effect estimate | p-value |
|---|---|---|---|---|

No local reactions at the injection site (wheals or erythema) were observed in either group.

# Discussion

Contrary to the expectation implied by parecoxib's role in multimodal analgesia, this pilot found that lidocaine with venous occlusion was substantially more effective than parecoxib with venous occlusion in preventing propofol injection pain. To our knowledge, these are the first data to compare the two agents directly for this indication.

The most striking feature of the result is not merely that parecoxib was inferior, but that it appeared to confer little benefit at all: the parecoxib incidence of 66.7% is essentially indistinguishable from the 60–70% typically reported for propofol given without any pretreatment [3]. This is difficult to reconcile with the only prior trial of parecoxib for this indication (Ghai et al.), which used the same 40 mg dose and 120-second occlusion and reported an incidence of 26% (versus 40% at 20 mg and 58% with placebo) [5]. Our finding is therefore best understood as a failure to replicate that single study.

Several explanations merit consideration. Parecoxib is a prodrug with no intrinsic cyclo-oxygenase activity; it must first be converted to its active metabolite, valdecoxib, in order to inhibit COX-2. A local vascular effect of parecoxib was proposed in an intravenous regional analgesia study for complex regional pain syndrome, in which venous occlusion was maintained for five minutes; even there, the authors suggested the benefit might reflect slow release of parecoxib from the occluded segment with subsequent activation in the liver, rather than a genuine local effect [6]. This is consistent with the drug's established pharmacology: parecoxib is activated to valdecoxib by hepatic carboxylesterases — enzymes that are largely absent from peripheral tissues [7]. During a 120-second venous occlusion, parecoxib trapped at the injection site therefore has little opportunity to be converted to its active form, which offers a coherent explanation for the near-absent local effect observed here: unlike lidocaine, which acts directly and immediately, parecoxib cannot act at the time and place required. The site and timing of activation, rather than the dose, may thus determine whether parecoxib has any role in this setting.

Consistent with the wider literature, lidocaine with venous occlusion performed as expected: a quantitative systematic review identified it as the most effective single intervention [1], and a subsequent meta-analysis confirmed its superiority, particularly when combined with use of the antecubital vein, over pharmacological alternatives (opioids, NSAIDs, ketamine) and non-pharmacological measures (propofol temperature, injection speed, needle size) [3]. In our protocol, all other premedication was deferred until after pain assessment to remove confounding.

Notably, although parecoxib did not reduce the incidence of pain, the severity that did occur was frequently mild (median NRS 2), albeit with a tail extending into moderate-to-severe scores; parecoxib retains genuine value as a component of postoperative multimodal analgesia and opioid sparing — a role entirely separate from acute injection-pain prophylaxis.

# Strengths and limitations

Strengths include the randomized, double-blind design; a standardised, fixed 50 mg propofol challenge that equalises the pain stimulus across participants; standardisation of injection speed (over 5 seconds) and propofol temperature (room temperature), both recognised determinants of injection pain, removing them as confounders; the use of a single propofol formulation (1% medium-/long-chain triglyceride emulsion, Fresenius Kabi) identically in both arms, removing formulation as a between-group confounder; deferral of all other analgesia until after assessment; use of a validated NRS; and prospective registration with prior ethical approval. A further point strengthens interpretation: the MCT/LCT emulsion is itself associated with less injection pain than the older long-chain triglyceride preparation, so the incidence seen in the parecoxib arm — comparable to historical untreated rates — is unlikely to be an artefact of a particularly painful

| Outcome | Lidocaine (n = 15) | Parecoxib (n = 15) | Effect estimate | p-value |
|---|---|---|---|---|

preparation. Limitations include the small sample (n = 30), which limits precision and generalizability and yields wide confidence intervals, and the single-centre setting.

# Future directions

Larger, multicentre studies would strengthen the generalizability of these findings. Because the mechanistic considerations above point to occlusion duration and timing rather than dose, future work should test parecoxib with a longer occlusion or earlier administration to allow fuller local COX-2 inhibition, and should evaluate whether a parecoxib–lidocaine combination offers any synergistic benefit.

## Conclusion

In this pilot, parecoxib with venous occlusion did not reduce propofol injection pain compared with lidocaine and performed comparably to historical untreated rates. These preliminary data support lidocaine with venous occlusion as the preferred pretreatment for propofol injection pain. These findings should be considered preliminary and warrant confirmation in a larger, adequately powered multicentre trial. Parecoxib's established value in multimodal analgesia is unaffected by these findings; it simply does not appear, at this dose and occlusion time, to be an effective measure for preventing pain on propofol injection.

**Tables**

# Figures

## Abbreviations

ARR
Absolute risk reduction
ASA
American Society of Anesthesiologists
CI
Confidence interval
CONSORT
Consolidated Standards of Reporting Trials
COX-2
Cyclooxygenase-2
ECG
Electrocardiography
IQR
Interquartile range
MCMSS
Medical City Hospital for Military and Security Services
MCT/LCT
Medium-chain triglyceride/long-chain triglyceride
NNT
Number needed to treat
NRS
Numerical rating scale
NSAIDs
Non-steroidal anti-inflammatory drugs
RR
Relative risk
SD

| Outcome | Lidocaine (n = 15) | Parecoxib (n = 15) | Effect estimate | p-value |
|---|---|---|---|---|

Standard deviation
SPSS
Statistical Package for the Social Sciences.

# Declarations

### Ethics approval and consent to participate

The study protocol and conduction were approved by the Medical Research Ethics Committee of the Medical City for Military and Security Services (MCMSS-MREC), Oman (Approval Code: MCMSS-MREC 023/2025; dated 22 July 2025). All procedures involving human participants were conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Written informed consent to participate was obtained from all participants prior to enrolment. The trial was registered on ClinicalTrials.gov (NCT07116304) before enrolment of the first participant.

### Consent for publication

Not Applicable.

### Availability of data and materials

The data collected and analysed during this study, and the study protocol, are available from the first author on reasonable request, subject to applicable ethical and institutional requirements. No separate statistical analysis plan was prepared.

### Competing Interests

The authors declare no competing interests.


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# Authors' contributions

MH Al-Rashdi and F Al-Hinai wrote the abstract, introduction, methods, discussion and conclusion. K Al Mandhari and AO Mohamed analysed and wrote the results with the help of a statistician from Oman Medical Specialty Board. MH Al-Rashdi and S Al-Abri prepared the tables and figures.

All authors helped in collecting data. All authors reviewed the manuscript.


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# References


1. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90(4):963–9.
2. Scott RPF, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. Anaesthesia. 1988;43(6):492–4.

| Outcome | Lidocaine (n = 15) | Parecoxib (n = 15) | Effect estimate | p-value |
|---|---|---|---|---|


3. Jalota L, Kalira V, George E, Shi Y, Hornuss C, Radke O, Pace NL, Apfel CC. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011;342:d1110.
4. Product information. Dynastat (parecoxib sodium). Therapeutic Goods Administration; 2024.
5. Ghai B, Makkar JK, Bala I, Wig J. Effect of parecoxib pretreatment and venous occlusion on propofol injection pain: a prospective, randomized, double-blinded, placebo-controlled study. J Clin Anesth. 2010;22(2):88–92.
6. Frade LCP, Lauretti GR, Lima ICPR, Pereira NL. The antinociceptive effect of local or systemic parecoxib combined with lidocaine/clonidine intravenous regional analgesia for complex regional pain syndrome type I in the arm. Anesth Analg. 2005;101(3):807–11.
7. Nestor CC, Ng C, Sepulveda P, Irwin MG. Pharmacological and clinical implications of local anaesthetic mixtures: a narrative review. Anaesthesia. 2022;77(3):339–50.


# Figures

**Figure 1.** CONSORT flow diagram. Pre-randomization screening counts were not recorded, so the flow begins at randomization:

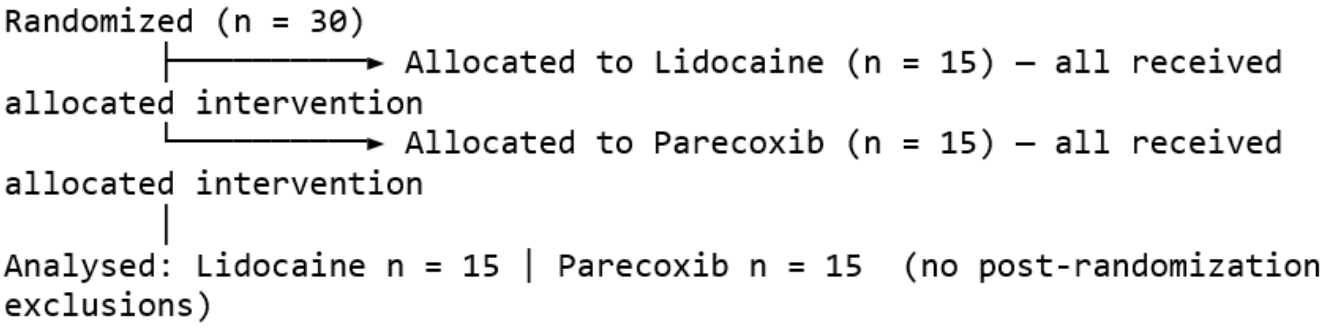



**Figure 1**

See image above for figure legend.