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REVIEW

Comparative Effectiveness of Pharmacological, Non-Pharmacological, and Combined Strategies for Pain Relief During Colonoscopy: A Bayesian Network Meta-Analysis of Randomized Trials

Xiaonan Huang[1,*], Shan Tian[2,*], Lifan Xu[1,*], Juhan Chen[1,*], Hao Wang[3], Tingting Mai[1], Lei Shi[1], Han Wang[4], Mengcheng Cai[5], Fanfu Fang[1]

[1]Department of Rehabilitation Medicine, Changhai Hospital, Naval Medical University, Shanghai, People's Republic of China; [2]Department of Acupuncture and Massage, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [3]Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, People's Republic of China; [4]School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, People's Republic of China; [5]Department of Rehabilitation Medicine, Naval Medical Center, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Fanfu Fang; Mengcheng Cai, Changhai Hospital, Naval Medical University, 168 Changhai Road, Yangpu District, Shanghai, 200433, People's Republic of China, Email fangfanfu@126.com; caimengcheng@126.com

Background: Colonoscopy is the gold standard for colorectal cancer screening, but procedural pain remains a major barrier to patient compliance. Various pharmacological and non-pharmacological interventions have been developed to improve patient comfort, yet the comparative effectiveness of these strategies remains unclear.

Methods: We systematically searched five databases for randomized controlled trials published between 2004 and 2024 that evaluated analgesic interventions for colonoscopy and performed a Bayesian random-effects network meta-analysis. We analyzed two pre-specified subnetworks—non-pharmacological and pharmacological/combined—according to intervention type. The primary outcome was pain on a visual analogue scale.

Results: 40 RCTs (5614 participants, 32 interventions) were included. Compared to blank control: 1) Combined physical intervention + analgesia/sedation (MD = −2.7, 95% CrI: −5.3 to −0.15) and water perfusion/CO_2 insufflation (MD = −1.9, 95% CrI: −2.8 to −0.99) significantly reduced pain; 2) Among non-pharmacological interventions, CO_2 insufflation, water perfusion, and visual distraction showed significant advantages; 3) Among pharmacological/combined interventions, pethidine + benzodiazepines + non-pharmacological (MD = −5.1, 95% CrI: −8.6 to −1.7) and propofol-based strategies were most effective. SUCRA rankings identified combined physical intervention + analgesia/sedation, propofol, and water perfusion/CO_2 as top overall interventions.

Conclusion: Multimodal strategies that combine pharmacological agents, especially pethidine or propofol, with non-pharmacological techniques such as CO_2 insufflation and water perfusion provide the most effective pain relief during colonoscopy.

Keywords: colonoscopy, pain relief, network meta-analysis, nonpharmacologic interventions, randomized controlled trials

Introduction

According to recent statistics, there were approximately 1.92 million new cases of colorectal cancer (CRC) worldwide in 2022, accounting for 10.2% of all malignancies, with 904,000 deaths representing 9.3% of cancer-related mortality. CRC ranks third in incidence and second in mortality among all cancers globally.[1] Notably, the incidence of CRC among individuals under the age of 50 has been steadily increasing, with the median age at diagnosis for early-onset CRC in the United States declining from 72 to 66 years.[2] Furthermore, it is projected that by 2030, the annual global incidence of CRC will reach 2.2 million cases, with China's share likely to further increase.[3]

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Colonoscopy remains the gold standard for CRC screening, enabling early detection of 45–75% of colorectal cancers and reducing CRC-related mortality by nearly 50%.[4] Regular colonoscopic screening every 2–3 years substantially increases the likelihood of early diagnosis and can slow disease progression. However, data indicate that as many as 16–20% of routine colonoscopies are prematurely terminated due to intolerable pain. This discomfort—primarily resulting from colonic traction, abdominal distension, and spasm—significantly impairs patient compliance, as fear of pain leads many patients to avoid recommended repeat examinations.[5] Poor adherence to colonoscopy due to anticipated or experienced pain can reduce lesion detection, delay diagnosis, and worsen outcomes, underscoring the need for effective, scalable analgesia.[6]

To address the wide range of adjunctive analgesic approaches used to improve patient tolerance during colonoscopy, we designed our analysis at the strategy level rather than at the level of individual interventions. We conducted a network meta-analysis, which integrates both direct and indirect comparisons to evaluate multiple strategies when head-to-head trials are limited.[7] Before analysis, all trial arms were pre-classified into three strategy types: non-pharmacological,[8] pharmacological, and combined approaches integrating both.[9] Because pharmacological trials typically employed placebo controls whereas non-pharmacological trials often used blank controls, we structured the evidence into two subnetworks, non-pharmacological and pharmacological/combined, to respect heterogeneous control types, minimize transitivity violations, and reduce network sparsity.[10] Accordingly, this review evaluates analgesia at the strategy level—non-pharmacological, pharmacological, and combined—rather than single agents, to inform resource-sensitive, patient-tailored practice.

Methodology

Study Design

This Bayesian network meta-analysis was conducted and reported in accordance with the PRISMA-NMA guidelines.[11] The protocol was prospectively registered in PROSPERO (www.crd.york.ac.uk, CRD42024586361).

Search Strategy

This study systematically reviewed randomized controlled trials (RCTs) evaluating analgesic interventions for colonoscopy. Comprehensive literature searches were conducted in five databases: Web of Science, PubMed, Embase, Cochrane CENTRAL, and ClinicalTrials.gov. Boolean operators were used to combine MeSH terms and free-text keywords, and the search strategy was constructed according to the PICOS framework, with the study type limited to RCTs (for detailed search strategies, see Table 1s). The search covered publications from November 7, 2004, to November 7, 2024, without language restrictions; non-English articles were included after translation. Reference management was performed using EndNote 20 to remove duplicates, followed by an additional manual deduplication step. Titles and abstracts were screened to exclude irrelevant studies, and the full texts of the remaining articles were reviewed for eligibility and systematically assessed to determine the final inclusion set.

Based on preliminary literature review, we observed that analgesic strategies in colonoscopy include pharmacological, non-pharmacological, and combined interventions, with numerous possible permutations. Therefore, for all included studies, we initially grouped similar intervention types before analysis, and then categorized them into two major groups: (1) interventions containing only non-pharmacological modalities, and (2) interventions involving pharmacological agents or combined treatments. This approach aimed to ensure greater objectivity and clarity in the network meta-analysis, and to provide clinically relevant guidance for analgesic strategies during colonoscopy.

Inclusion and Exclusion Criteria

First, we included studies involving complete colonoscopy procedures, regardless of whether anesthesia was used, and excluded trials focused solely on rectal or colonic insufflation. Studies involving sequential upper and lower gastrointestinal endoscopy (ie, combined gastroscopy and colonoscopy) were also excluded. Second, with respect to interventions, we excluded studies where differences in operator expertise (among endoscopists or anesthesiologists) or variations in endoscopic equipment could affect pain outcomes. All external patient analgesic interventions—both

pharmacological and non-pharmacological—were eligible for inclusion. Regarding outcome measures, only studies reporting pain scores as a primary or secondary outcome were included. We also collected data on secondary outcomes that may indirectly reflect pain, such as anxiety and patient satisfaction, as well as dosages of sedatives or analgesics used in studies involving such medications. Finally, to minimize bias arising from temporal differences in operator or equipment proficiency, we limited our review to RCTs published within the past 20 years, and excluded any non-randomized clinical studies. Study selection was performed independently by two reviewers (HXN and XLF). Any disagreements were resolved through discussion, or if necessary, in consultation with a third reviewer (TS).

Data Extraction Procedures

For each eligible study, two reviewers (HXN and XLF) independently extracted the following data: inclusion and exclusion criteria, patient demographic characteristics (including sex and age), intervention details, intervention duration, and dosage. Patient outcomes assessed in this study included pain scores measured by the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), and all other potential indicators reflecting pain severity, such as intubation success rate, sedative and analgesic usage, anxiety levels, and patient satisfaction, along with their corresponding means and standard deviations. When studies reported median and interquartile range, these values were converted to mean and standard deviation using established methods,[12,13] Adverse events related to analgesic interventions were also recorded. In studies reporting pain at multiple time points, the pain score corresponding to the moment of greatest discomfort during the procedure was prioritized for analysis. If intra-procedural pain scores were not available, the first pain score assessed immediately after the procedure was used.

Risk of Bias

For all included RCTs, two reviewers (HXN and XLF) independently assessed the risk of bias using the Cochrane Risk of Bias tool 2.0 (version: ROB2_cluster_beta_v3).[14] Discrepancies were resolved by discussion or, if necessary, in consultation with a third reviewer.

Statistical Analysis

To compare the effectiveness and safety of different analgesic interventions during colonoscopy, a network meta-analysis was performed using the gemtc package in R (version 4.3.3). A Bayesian random-effects network meta-analysis was used to estimate the relative effects of all interventions. This approach, utilizing a design-by-treatment interaction model, assessed the consistency assumption across the entire network, while node-splitting methods evaluated local inconsistency between direct and indirect evidence within each closed loop of the network.[15]

The relative effectiveness of interventions was comprehensively evaluated using the gemtc and netmeta packages in R. First, data were organized into tables containing study IDs, group sample sizes, means, standard deviations, and other relevant continuous variables. The mtc.network function was used to construct the network evidence map. For statistical modeling, a consistency model was applied, assuming that direct and indirect comparisons yield consistent results. Parameters were estimated using the Markov chain Monte Carlo (MCMC) algorithm, with four chains, 10,000 burn-in iterations, 50,000 sampling iterations, and a thinning interval of 10 to reduce autocorrelation. Model convergence was evaluated with trace plots, density plots, and the Gelman-Rubin statistic. Heterogeneity was assessed using a random-effects model, and quantified by the I^2 statistic; $I^2 > 50\%$ was considered indicative of substantial heterogeneity. Local inconsistency was examined using the node-splitting method by comparing direct and indirect evidence; a $P < 0.05$ was considered indicative of significant inconsistency. Global inconsistency was assessed using the design-by-treatment interaction model via the mtc.anohe function. Treatment ranking was determined using the surface under the cumulative ranking curve (SUCRA), with values ranging from 0 to 1, where higher values indicate better ranking.[16] The rank.probability function was used to generate rank probability matrices, and cumulative probability plots and rankograms were created using the ggplot2 package.

Equity, Diversity and Inclusion Statement

Our study included RCTS of colonoscopy pain studies with no exclusion criteria for sex, race, ethnicity, and socio-economic level. Our research team consisted of individuals working in Shanghai, China, including three women and four men from different disciplines (pain management, colorectal surgery, rehabilitation, and medical research).

Results

Study Selection

A total of 6820 records were identified from five databases (see Tables 2s–4s for search strategies). After automatic and manual deduplication using EndNote, 2237 duplicates were removed. The titles and abstracts of the remaining 4583 records were screened, leaving 181 articles for full-text review. Following the exclusion of 141 studies upon full-text assessment, 40 articles were ultimately included in the network meta-analysis[17–56] (see Figure 1 for the study selection flowchart). Of these, 35 were two-arm studies, three were three-arm studies, and two were four-arm studies, encompassing a total of 5614 participants. Among these, 3070 were male (54.68%), with a mean age of 58.36 years.

Across the 40 included studies, 32 different interventions were identified. The most frequently used were blank control (22 studies), fentanyl combined with midazolam (8), water perfusion (7), virtual reality (VR, 5), electrical stimulation/electroacupuncture (4), propofol (4), visual distraction (3), music (3), placebo (3), CO_2 (2), abdominal compression (2), fentanyl plus propofol (2), music plus fentanyl and propofol (2), and pethidine plus midazolam (2). The remaining interventions—including various combinations of CO_2, dezocine, diazepam, pethidine, propofol, VR, music, nalbuphine, pentazocine, and dezocine—each appeared in one study. Of the included RCTs, 22 studies evaluated non-pharmacological interventions only, 17 involved pharmacological or combined interventions, and one study included non-pharmacological, pharmacological, and combined interventions. Detailed data for each study are provided in Table 5s.

Network Geometry

The 40 included RCTs were initially categorized into 12 groups (Figure 2a), including one blank control group and one placebo group, the specific intervention methods included in each category are shown in Table 6s. In the non-pharmacological subgroup, 22 non-pharmacological RCTs and the non-pharmacological arm of one mixed-intervention study were divided into nine groups, including blank control and placebo (Figure 2b). For pharmacological interventions, 17 RCTs (plus the pharmacological arm of one mixed study) were also divided into nine groups, including a placebo group (Figure 2c).

Risk of Bias

For the primary outcome, most studies were rated as having "some concerns" for risk of bias (n = 23, 57.5%). High risk of bias was identified in 4 studies (10%), while 13 studies (32.5%) were judged as low risk. The greatest risks were observed in the domains of measurement of outcomes and deviations from intended interventions. Full details of the risk of bias assessment are provided in Figure 1s.

Bayesian Model results for Pain Scores

Following network construction, a Bayesian random-effects consistency model was used for statistical analysis. The model specified a normal likelihood function and identity link, assuming consistency between direct and indirect comparisons. Four Markov chains were run with 10,000 burn-in iterations and 50,000 sampling iterations (thinning interval = 10) for parameter estimation. Gelman-Rubin diagnostic plots and trace plots confirmed adequate convergence of all parameters (potential scale reduction factors <1.05), indicating satisfactory model fit for all three comparison sets. Node-splitting and random-effects models were applied to assess local inconsistency within each evidence loop. The inconsistency tests for all interventions revealed that most pairwise comparisons did not show significant inconsistency; after separating analyses by pharmacological and non-pharmacological interventions, all pairwise comparisons were consistent (see Figures 2s–4s). Finally, the global heterogeneity of the three networks was evaluated using the design-by-

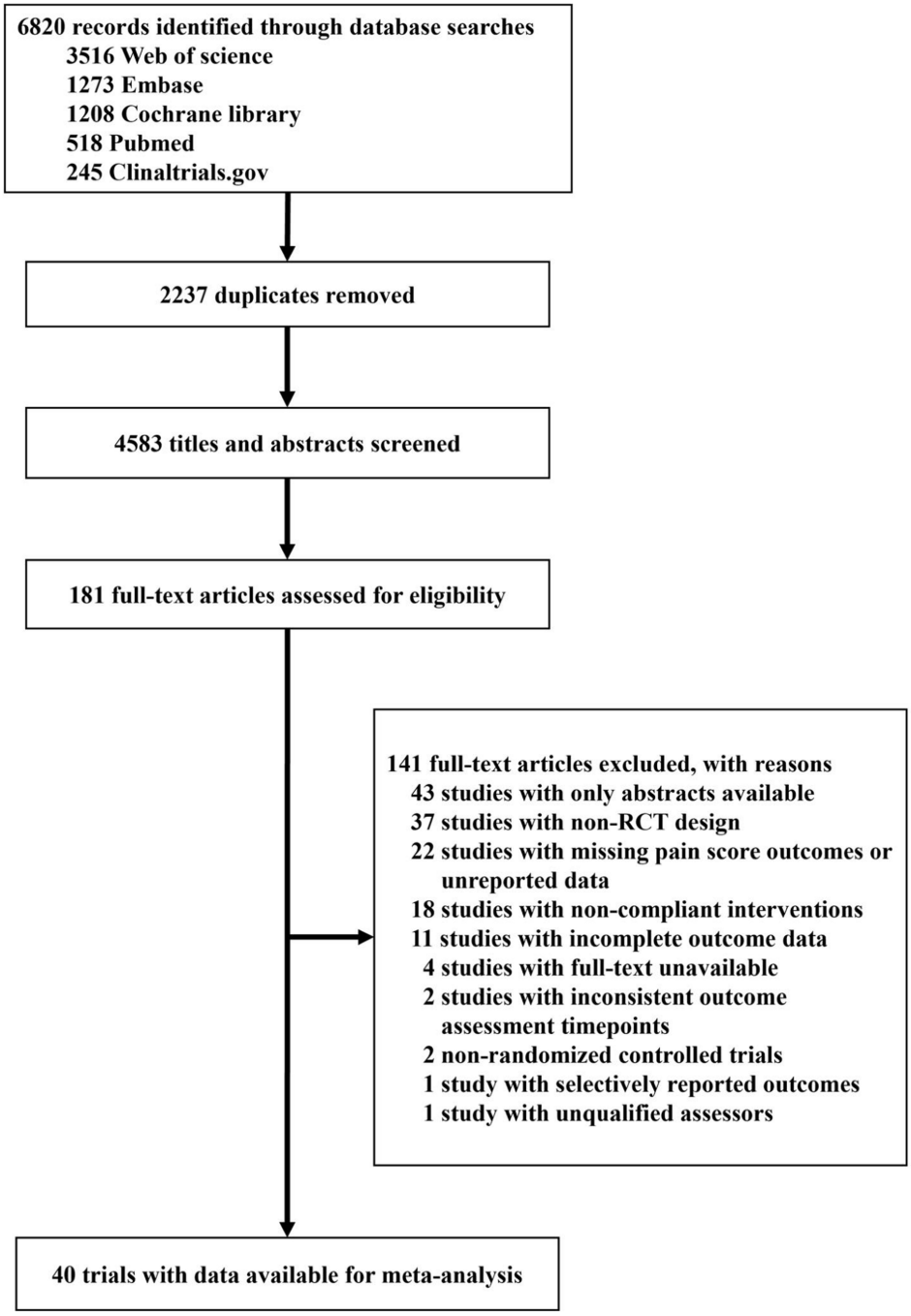

Figure 1 Flow chart of studies identified and included in the network meta-analysis.

treatment interaction model, revealing high overall heterogeneity, with I^2 values of 95.71%, 93.75%, and 99.62%, respectively.

All Intervention Measures

Compared to blank control, both physical interventions combined with analgesia and sedation (MD = −2.7, 95% CrI: −5.3 to −0.15) and water perfusion/CO_2 insufflation (MD = −1.9, 95% CrI: −2.8 to −0.99) demonstrated significant reductions in pain scores. In addition, distraction alone (MD = −0.97, 95% CrI: −1.8 to −0.19) was also associated with a statistically significant reduction in pain (Figure 5s). Other interventions—including propofol (MD = −2.1, 95% CrI:

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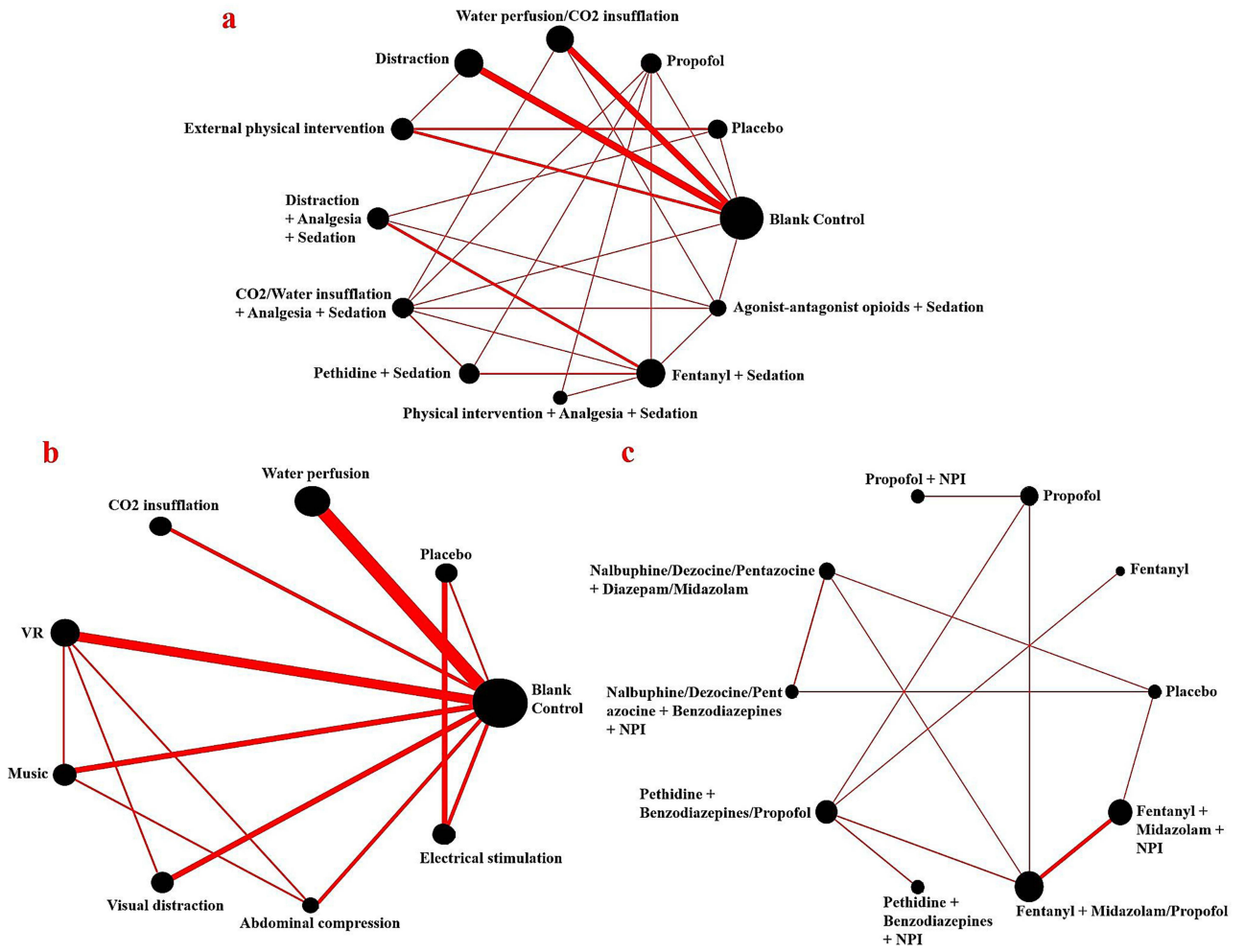

Figure 2 The network structure diagram. (**a**) All intervention measures; (**b**) Non-pharmacological intervention measures; (**c**) Pharmacological and combined intervention measures. Each node represents an intervention and is weighted by the number of studies that received the intervention. Each line connecting the nodes is weighted by the number of studies that included a pairwise comparison.
Abbreviations: NPI, Non-pharmacological intervention.

−4.3 to 0.082), pethidine plus sedatives (MD = −1.7, 95% CrI: −3.7 to 0.43), and fentanyl plus sedatives (MD = −1.4, 95% CrI: −3.3 to 0.49)—showed a trend toward pain relief, though these results did not reach statistical significance (Table 1). The league table of all interventions uses orange shading to indicate that the intervention listed in the row is more effective than that in the column, while blue indicates the opposite. We divided the yellow and blue shading into four tiers. For yellow: the first tier applies when MD exceeds 3 points. The second tier applies when MD is below 3 points and the 95% CrI has a lower bound greater than 0 and an upper bound greater than 3 points. The third tier applies when the 95% CrI has a lower bound greater than 0 and an upper bound between 1 and 3 points. The fourth tier applies when MD is below 3 points and the 95% CrI has a lower bound less than or equal to 0. For blue, the rules are the reverse. Calculation methods are detailed in Figure 8s.

Non-Pharmacological Intervention Measures

CO_2 insufflation (MD = −1.9, 95% CrI: −3.7 to −0.14), water perfusion (MD = −1.7, 95% CrI: −2.7 to −0.70), and visual distraction (MD = −1.2, 95% CrI: −2.6 to −0.30) each showed significant advantages for pain relief (Figure 6s). Other interventions—including music (MD = −1.3, 95% CrI: −2.7 to 0.17), electrical stimulation (MD = −1.0, 95% CrI: −2.9 to 0.82), virtual reality (VR; MD = −0.73, 95% CrI: −1.9 to 0.36), and abdominal compression (MD = −0.53, 95% CrI: −2.2

Table 1 League Tables of All Mean Differences and 95% Confidence Intervals by All Interventions

Blank Control											
−0.9 (−2.5, 0.7)	Placebo										
2.1 (−0.1, 4.3)	3 (0.6, 5.4)	Propofol									
1.9 (1, 2.8)	2.8 (1, 4.6)	−0.2 (−2.5, 2)	Water perfusion/CO_2 insufflation								
1 (0.2, 1.8)	1.9 (0.2, 3.7)	−1.1 (−3.5, 1.2)	−0.9 (−2.1, 0.3)	Distraction							
0.8 (−0.3, 2)	1.8 (0.3, 3.2)	−1.3 (−3.6, 1.1)	−1 (−2.5, 0.4)	−0.1 (−1.5, 1.2)	External physical intervention						
1.2 (−0.7, 3.2)	2.2 (0.3, 4.2)	−0.9 (−2.7, 1)	−0.6 (−2.6, 1.4)	0.3 (−1.8, 2.4)	0.4 (−1.6, 2.4)	Distraction + A + S					
1.9 (0, 3.8)	2.8 (0.7, 5)	−0.2 (−1.8, 1.3)	0 (−1.9, 1.9)	0.9 (−1.2, 2.9)	1 (−1.1, 3.1)	0.6 (−1.1, 2.3)	CO_2/Water insufflation + A + S				
1.7 (−0.4, 3.8)	2.6 (0.3, 4.9)	−0.5 (−2, 1.1)	−0.2 (−2.3, 1.9)	0.7 (−1.5, 2.9)	0.8 (−1.5, 3.1)	0.4 (−1.3, 2.2)	−0.2 (−1.5, 1.1)	Pethidine + S			
2.7 (0.1, 5.3)	3.6 (0.9, 6.4)	0.6 (−1.2, 2.5)	0.8 (−1.8, 3.5)	1.7 (−1, 4.4)	1.9 (−0.8, 4.6)	1.5 (−0.8, 3.7)	0.8 (−1.3, 3)	1.1 (−1, 3.2)	Physical intervention + A + S		
1.4 (−0.5, 3.3)	2.3 (0.3, 4.4)	−0.7 (−2.2, 0.7)	−0.5 (−2.4, 1.5)	0.4 (−1.6, 2.5)	0.5 (−1.6, 2.6)	0.1 (−1.1, 1.4)	−0.5 (−1.9, 0.9)	−0.3 (−1.6, 1)	−1.3 (−3.2, 0.5)	Fentanyl + S	
0.6 (−1.2, 2.4)	1.6 (−0.5, 3.7)	−1.5 (−3.5, 0.5)	−1.2 (−3.1, 0.6)	−0.3 (−2.3, 1.6)	−0.2 (−2.2, 1.8)	−0.6 (−2.2, 1)	−1.2 (−3, 0.5)	−1 (−2.9, 0.8)	−2.1 (−4.5, 0.3)	−0.7 (−2.3, 0.8)	Agonist-antagonist opioids + S

Notes: Yellow shading indicates that the row intervention is superior to the column intervention, with darker shades representing larger benefits. Blue shading indicates the opposite. Each color is divided into four intensity tiers. For yellow: tier 1 applies when MD > 3 (darkest); tier 2 when MD < 3 and the 95% CrI has a lower bound > 0 and an upper bound > 3; tier 3 when the 95% CrI has a lower bound > 0 and an upper bound between 1 and 3; tier 4 when MD < 3 and the 95% CrI has a lower bound ≤ 0 (lightest). Blue shading follows the same rules in the opposite direction.

Abbreviations: A, Analgesia; S, Sedation.

to 1.2) did not reach statistical significance. The league table further presents pairwise comparisons among non-pharmacological interventions (Table 2).

Pharmacological and Combined Intervention Measures

The most effective pain relief was observed with pethidine plus benzodiazepines and non-pharmacological interventions (MD = −5.1, 95% CrI: −8.6 to −1.7). Similarly, propofol combined with non-pharmacological interventions was associated with significant pain reduction (MD = −4.4, 95% CrI: −8.1 to −0.75). Other interventions with significant advantages included propofol alone (MD = −3.9, 95% CrI: −7.0 to −0.80), pethidine plus benzodiazepines/propofol (MD = −3.7, 95% CrI: −6.7 to −0.84), and fentanyl plus midazolam plus non-pharmacological interventions (MD = −2.9, 95% CrI: −5.2 to −0.61) (Figure 7s). Fentanyl plus midazolam/propofol (MD = −2.3, 95% CrI: −4.7 to 0.016) demonstrated a trend toward pain reduction but did not reach statistical significance. Finally, combinations involving nalbuphine, dezocine, or pentazocine (with benzodiazepines and non-pharmacological interventions, or with diazepam/midazolam) were less effective (Table 3).

Superiority of Ranking

Figure 3 presents the SUCRA curves for all interventions. For all interventions combined (Figure 3a), the top three in terms of probability of being the best for pain relief were physical intervention plus analgesia and sedation (92.8%), propofol (81.2%), and water perfusion/CO_2 insufflation (76.7%). Additionally, CO_2/water perfusion plus analgesia and sedation (75.2%) and pethidine plus sedatives (66.8%) also showed high efficacy. For non-pharmacological interventions (Figure 3b), SUCRA analysis identified CO_2 insufflation (88.0%) as the most effective strategy, followed by water perfusion (85.9%), with music (70.3%) and visual distraction (66.5%) also ranking highly. Finally, among pharmacological and combined interventions (Figure 3c), pethidine plus benzodiazepines and non-pharmacological interventions ranked highest (97.4%) for pain relief, followed by propofol plus non-pharmacological interventions (86.2%) and propofol alone (76.8%). Pethidine plus benzodiazepines/propofol (73.1%) and fentanyl plus midazolam plus non-pharmacological interventions (57.2%) were next in efficacy.

Discussion

In this comprehensive network meta-analysis of analgesic interventions for colonoscopy, multimodal strategies that combine pharmacological sedation, opioid analgesics, and non-pharmacological approaches yielded the most pronounced pain relief. Notably, the combination of pethidine with benzodiazepine sedatives and adjunctive physical interventions (such as CO_2 insufflation or water perfusion) was associated with the highest efficacy. Deep sedation with propofol alone also emerged as one of the most effective single interventions, underscoring the potent analgesic and amnesic effects of deep sedation. Among non-pharmacological interventions, CO_2 insufflation and water-aided techniques demonstrated significant analgesic benefits, ranking highest among standalone strategies. By contrast, standard moderate sedation regimens (such as fentanyl combined with midazolam) showed significant pain reduction compared to placebo but were less effective than multimodal drug-based strategies, possibly due to variation in drug dosing—some studies used minimum dosages, while others utilized patient-controlled sedation. Importantly, many pairwise differences had overlapping credible intervals, indicating some uncertainty regarding the precise rank order. Overall, combinations of analgesic modalities delivered the greatest pain relief, highlighting the need for individualized pain management by anesthesiologists and endoscopy nurses, particularly in older patients undergoing surveillance after colorectal cancer surgery, where careful attention to both drug dosages and non-pharmacological approaches is warranted.

Colonoscopy-related pain primarily arises from two sources: mechanical stretching caused by the endoscope and luminal distension due to insufflation. The non-pharmacological interventions examined in this study directly address these pain mechanisms. Replacing air with CO_2 for insufflation alleviates discomfort, as CO_2 is rapidly absorbed from the bowel, reducing luminal distension and bloating.[57] There is evidence that water perfusion and CO_2 insufflation, compared to air, significantly reduce colonoscopy-related pain and discomfort.[58] Our analysis confirmed that CO_2 insufflation resulted in significantly lower pain scores and improved patient comfort compared to air. Similarly, water-aided techniques (including water immersion and water exchange) reduce pain by minimizing mesenteric traction,

Table 2 League Tables of All Mean Differences and 95% Confidence Intervals by Nonpharmacological Interventions

Blank Control								
−0.9 (−3.1, 1.3)	Placebo							
1.7 (0.7, 2.7)	2.6 (0.2, 5)	Water perfusion						
1.9 (0.1, 3.7)	2.8 (0, 5.7)	0.2 (−1.8, 2.2)	CO2 insufflation					
0.7 (−0.3, 1.9)	1.6 (−0.8, 4.1)	−1 (−2.4, 0.5)	−1.2 (−3.3, 0.9)	VR				
1.3 (−0.2, 2.7)	2.2 (−0.4, 4.8)	−0.4 (−2.2, 1.3)	−0.7 (−3, 1.7)	0.5 (−1.2, 2.2)	Music			
1.2 (−0.3, 2.6)	2.1 (−0.6, 4.7)	−0.6 (−2.3, 1.3)	−0.8 (−3.1, 1.6)	0.4 (−1.3, 2.1)	−0.1 (−2.1, 1.9)	Visual distraction		
0.5 (−1.2, 2.2)	1.5 (−1.3, 4.2)	−1.2 (−3.1, 0.8)	−1.4 (−3.8, 1.1)	−0.2 (−2.1, 1.6)	−0.7 (−2.8, 1.3)	−0.6 (−2.9, 1.6)	Abdominal compression	
1 (−0.8, 2.9)	1.9 (0.3, 3.5)	−0.7 (−2.8, 1.4)	−0.9 (−3.5, 1.7)	0.3 (−1.9, 2.4)	−0.2 (−2.6, 2.1)	−0.1 (−2.5, 2.2)	0.5 (−2, 3)	Electrical stimulation

Notes: Color coding: Yellow shading indicates that the row intervention is superior to the column intervention, with darker shades representing larger benefits. Blue shading indicates the opposite. Each color is divided into four intensity tiers. For yellow: tier 1 applies when MD > 3 (darkest); tier 2 when MD < 3 and the 95% CrI has a lower bound > 0 and an upper bound > 3; tier 3 when the 95% CrI has a lower bound > 0 and an upper bound between 1 and 3; tier 4 when MD < 3 and the 95% CrI has a lower bound ≤ 0 (lightest). Blue shading follows the same rules in the opposite direction.

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Table 3 League Tables of All Mean Differences and 95% Confidence Intervals by Pharmacological and Combined Interventions

Placebo								
3.9 (0.8, 7.1)	Propofol							
4.4 (0.7, 8.1)	0.5 (−1.4, 2.4)	Propofol + NPI						
1.8 (−0.4, 3.9)	−2.1 (−5.2, 0.9)	−2.6 (−6.3, 1)	Nalbuphine/Dezocine/Pentazocine + Diazepam/ Midazolam					
1.7 (−0.7, 4)	−2.2 (−5.7, 1.1)	−2.7 (−6.7, 1.1)	−0.1 (−2, 1.7)	Nalbuphine/Dezocine/Pentazocine + Benzodiazepines + NPI				
3.7 (0.8, 6.6)	−0.2 (−2.3, 1.9)	−0.7 (−3.5, 2.1)	1.9 (−0.9, 4.8)	2.1 (−1.2, 5.2)	Pethidine + Benzodiazepines/ Propofol			
5.1 (1.6, 8.6)	1.2 (−1.6, 4)	0.7 (−2.7, 4)	3.3 (−0.1, 6.7)	3.4 (−0.3, 7.1)	1.4 (−0.5, 3.3)	Pethidine + Benzodiazepines + NPI		
2.4 (0, 4.7)	−1.6 (−3.7, 0.5)	−2.1 (−4.9, 0.7)	0.6 (−1.7, 2.8)	0.7 (−2, 3.4)	−1.4 (−3.1, 0.3)	−2.7 (−5.3, −0.2)	Fentanyl + Midazolam/ Propofol	
2.9 (0.6, 5.1)	−1 (−3.4, 1.3)	−1.5 (−4.6, 1.5)	1.1 (−1.3, 3.5)	1.2 (−1.5, 4)	−0.8 (−2.9, 1.2)	−2.2 (−5, 0.6)	0.5 (−0.6, 1.7)	Fentanyl + Midazolam + NPI

Notes: Color coding: Yellow shading indicates that the row intervention is superior to the column intervention, with darker shades representing larger benefits. Blue shading indicates the opposite. Each color is divided into four intensity tiers. For yellow: tier 1 applies when MD > 3 (darkest); tier 2 when MD < 3 and the 95% CrI has a lower bound > 0 and an upper bound > 3; tier 3 when the 95% CrI has a lower bound > 0 and an upper bound between 1 and 3; tier 4 when MD < 3 and the 95% CrI has a lower bound ≤ 0 (lightest). Blue shading follows the same rules in the opposite direction.
Abbreviation: NPI, Non-pharmacological intervention.

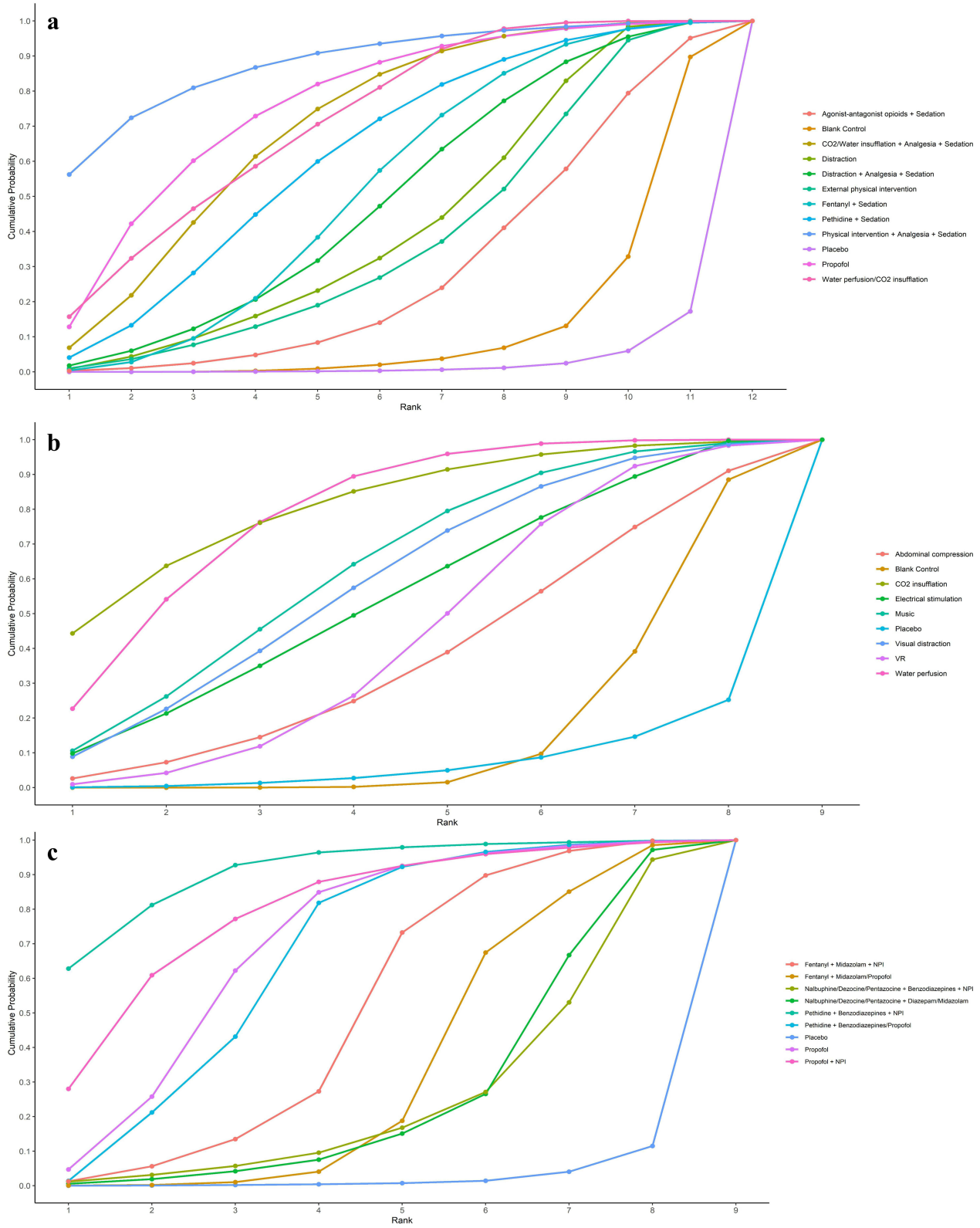

Figure 3 Probability of ranking for each intervention for outcomes. (**a**) All intervention measures; (**b**) Non-pharmacological intervention measures; (**c**) Pharmacological and combined intervention measures.
Abbreviations: NPI, Non-pharmacological intervention.

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maintaining minimal luminal distension, and facilitating easier advancement with fewer loop formations, thereby improving tolerance.[59] These mechanisms explain why CO_2 and water perfusion ranked as top non-pharmacological interventions in our study.

In terms of pharmacological options, deep sedation with propofol was highly effective. Previous studies have shown that patients report greater satisfaction with propofol compared to traditional benzodiazepine/opioid sedation, and there is a growing preference for propofol for colonoscopy sedation due to its rapid onset and potent analgesic effects.[26] Importantly, propofol has a safety profile comparable to traditional sedation, with meta-analyses showing no increase in cardiopulmonary complications compared to midazolam-fentanyl regimens.[60] Although propofol requires more intensive anesthesia support or monitoring, it represents an excellent option for providing a pain-free colonoscopy experience where resources allow. Among combined interventions, pethidine plus benzodiazepines with CO_2 or water perfusion was also highly effective. Fentanyl plus midazolam remains one of the most widely used sedation regimens worldwide, with well-established efficacy and safety. Although our network meta-analysis showed a trend toward pain reduction for this combination (MD = −2.3, 95% CrI: −4.7 to 0.016), this did not reach statistical significance. This finding does not imply a lack of efficacy—extensive evidence supports its use over unsedated colonoscopy—but likely reflects variability in dosing regimens and sedation protocols among studies.[26,29,31,43] In clinical practice, standard dosing of opioid and benzodiazepine combinations remains an effective method for moderate sedation during colonoscopy, though its analgesic efficacy may be inferior to propofol.

While other non-pharmacological interventions (such as distraction techniques and transcutaneous nerve stimulation) did not demonstrate significant pain reduction, they nonetheless contributed to improved patient tolerance. Music therapy and audiovisual distraction have been validated as simple, low-risk approaches to reduce anxiety and discomfort during colonoscopy. A recent meta-analysis concluded that music during colonoscopy enhances the patient experience and significantly reduces both pain and anxiety.[61] Our analysis similarly identified VR, music, and visual distraction as higher-ranking non-pharmacological strategies. By engaging patient attention and alleviating anxiety, distraction techniques likely enhance pain tolerance and procedure tolerability. Additionally, our results indicate that electrical stimulation and acupuncture, although not statistically significant, may offer supplementary analgesia. When combined with pharmacological interventions, these effects may be additive; for example, adjunctive use of TENS or acupuncture with sedation and analgesia could lower required drug doses and improve overall comfort. In clinical application, the number and type of combined interventions may be limited by available resources, but our findings highlight that multimodal analgesia is highly effective for colonoscopy.

Significant heterogeneity ($I^2 > 90\%$) was observed among studies, likely attributable to the large number of indirect comparisons, variations in intervention techniques (eg, water perfusion methods), non-standardized drug dosages, and differences in pain measurement timing and scales. Despite this heterogeneity, our network meta-analysis showed good overall consistency, with node-splitting analysis revealing no significant differences between direct and indirect evidence.

We stratified the analyses into non-pharmacological and pharmacological/combined subnetworksto improve clinical interpretability. First, control types differed across trials: sedative or analgesic studies typically used placebo controls such as saline, whereas non-pharmacological studies generally used blank controls such as no additional intervention with standard air insufflation. Mixing these would conflate expectation effects and risk bias. Second, placing all interventions into a single network would create an overly complex, sparsely connected geometry and yield imprecise or unstable estimates. Accordingly, Table 1 pools all interventions and necessarily includes both blank and placebo nodes with more indirect paths, whereas Table 3 restricts the evidence to pharmacological and combined arms with placebo as the primary comparator. Because control expectations and network connectivity differ, posterior estimates can legitimately shift without implying bias; for example, the effect for propofol versus placebo appears as 3.0 in all-interventions network and 3.9 in pharmacological/combined subnetwork, reflecting network geometry and evidence composition, which showed no important local inconsistency after subnetworking despite high global heterogeneity.

Our findings provide clear evidence-based guidance to improve patient comfort during colonoscopy. Key non-pharmacological methods—such as CO_2 insufflation and water-assisted techniques—are simple, cost-effective, and significantly reduce discomfort. CO_2 insufflation is especially recommended, as it has been proven to lessen post-procedure pain and bloating compared to traditional air insufflation. Water-assisted methods (immersion or exchange)

further reduce pain and are particularly valuable in settings with limited access to sedation or anesthesia. Where deep sedation is not feasible, moderate sedation with benzodiazepines and opioids remains effective. Combining pharmacological and non-pharmacological strategies can further enhance comfort.

Several limitations of this study should be acknowledged. Significant heterogeneity existed among included studies, likely resulting from differences in patient populations, intervention protocols, sedation regimens, and pain assessment methods. Additionally, interventions were grouped into broader categories to ensure feasibility, which may have masked differences between specific techniques or drug regimens. Our analysis focused only on procedural pain outcomes and did not assess other important endpoints such as anxiety, patient satisfaction, cecal intubation rate, or adenoma detection rate.

Conclusion

This network meta-analysis provides a comprehensive comparison of pharmacological, non-pharmacological, and combined interventions for pain management during colonoscopy. Our results demonstrate that combined interventions —particularly pethidine plus midazolam/propofol with CO_2 or water perfusion—are the most effective strategies for alleviating procedure-related pain. Among pharmacological approaches, pethidine plus midazolam/propofol and propofol alone showed the greatest analgesic efficacy. CO_2 insufflation and water perfusion were the most effective non-pharmacological options and can significantly reduce pain even in the absence of sedation. In settings with anesthesia support, multimodal strategies should be prioritized to maximize pain relief and completion. Where such resources are limited, CO_2 insufflation or water-aided methods provide effective, scalable options. Framing decisions at the strategy level aligns analgesia with local resources and patient preferences.

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Disclosure

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