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REVIEW ARTICALE

EVALUATING THE EFFICACY OF DICLOFENAC IN MANAGING POSTOPERATIVE SEQUELAE AFTER MANDIBULAR THIRD MOLAR EXTRACTION - A SYSTEMATIC REVIEW AND META-ANALYSIS

Anuroop Singhai MDS [1], Harshkant Gharote MDS [2], Rajanikanth Kambala MDS [3]

[1]Associate Professor, Clinical Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah - 21442, Saudi Arabia. PhD Scholar, Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College, Datta Meghe Institute of Higher Education and Research,Sawangi, Wardha, India. ORCID: 0000-0002-8806-1283
[2]Professor, Basic Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah - 21442, Saudi Arabia. PhD Scholar, Department of Oral Medicine and Radiology, Sharad Pawar Dental College, Datta Meghe Institute of Higher Education and Research, Sawangi, Wardha, India.ORCID: 0000-0002-3306-4962
[3]Professor, Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College, Datta Meghe Institute of Higher Education and Research, Sawangi, Wardha, India
Corresponding author: Dr. Anuroop Singhai, Associate Professor, Clinical Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah - 21442, Saudi Arabia. PhD Scholar, Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College, Datta Meghe Institute of Higher Education and Research, Sawangi, Wardha, India. Email: anuroopsinghai@gmail.com

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ABSTRACT

Objectives: Postoperative pain following mandibular third molar surgery is a prevalent and often debilitating condition that necessitates targeted pain management. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to alleviate this discomfort. This review aims to provide an updated synthesis of the current evidence on the efficacy and safety of diclofenac for managing postoperative pain after third molar surgery, by evaluating findings from relevant studies in the dental literature.

Materials and Methods: A literature search was conducted in PubMed and EBSCOhost databases until March 2025. The present systematic review assessed the effectiveness and safety of diclofenac for managing postoperative pain following third molar removal. Twenty-eight studies were included for review based on PRISMA guidelines. The review encompassed randomized controlled trials and clinical trials that examined postoperative pain management after mandibular third molar surgery.

Results: The present systematic review and meta-analysis included 24 studies. For statistical analysis, six study data for visual analogue scale (VAS) pain score were used. The pooled effect size of VAS pain scores was statistically not significant when compared to diclofenac versus other NSAIDs.

Conclusion: Diclofenac is a key analgesic for postoperative dental pain and has a favorable safety profile and efficacy. However, further research is needed to assess its long-term safety and efficacy in chronic pain management

Keywords: Diclofenac, efficacy, safety, postoperative pain, mandibular third molar

1. INTRODUCTION

From time immemorial clinical dental practice has relied heavily on the use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain management. Many drugs have been employed over the years with varying degrees of success in postoperative pain management.

The postoperative sequelae of third molar surgery are associated with pain, swelling and reduced mouth opening. Most patients are prescribed NSAIDs for the management of postoperative discomfort. However, each individual responds differently to the use of NSAIDs.

Over the years, combination therapy has become prevalent due to better postoperative outcomes.[1] NSAIDs are often prescribed in combination with anti-inflammatory enzymes or steroids to improve patient comfort and recovery.[2,3]

Effective pain management is crucial for improving postoperative outcomes and patient satisfaction. Diclofenac, a widely used NSAID, has been extensively studied for its role in alleviating postoperative dental pain. Diclofenac is a phenylacetic acid derivative product of rational drug design based on phenylbutazone, mefenamic acid, and indomethacin structures.[4] Structurally, two chlorine groups are present in the ortho position of the phenyl ring, locking the ring in maximal torsion that appears to be related to increased potency.

Diclofenac is known to exert its antinociceptive effect by inhibition of cyclooxygenase - 1 and - 2 enzymes responsible for producing prostaglandins.[5] Most of the adverse drug events associated with diclofenac are attributed to its mechanism of action. Clinicians are always wary of the serious gastrointestinal, cardiovascular and renal side effects that impact the outcome of therapy. Advances in pharmacotherapeutics have led to the alteration of the pharmacokinetic properties of oral diclofenac drug products that have several desirable characteristics, like convenient dosing, improved absorption, and rapid onset of analgesia.

With the advent of novel technology, drug particle size has been reduced for the development of low-dose oral diclofenac with good analgesic efficacy and considerably reduced systemic exposure.[6]

Properties of topical as well as injectable diclofenac have also been improved for a wider therapeutic range.[7]

1.1 Rationale

This review adopts an innovative narrative approach by synthesizing evidence from recent studies to provide a comprehensive assessment of the efficacy and safety profiles of various diclofenac formulations. It systematically evaluates how different dosing regimens and routes of administration influence clinical outcomes. Additionally, the review contextualizes diclofenac's performance in comparison to other non-steroidal anti-inflammatory drugs (NSAIDs), highlighting both its advantages and limitations.

This analysis aims to identify existing knowledge gaps, particularly regarding the long-term effects of diclofenac in diverse patient populations and the impact of novel formulations on therapeutic outcomes. By addressing these gaps, the review seeks to inform dental practitioners and guide future research directions in the field of dental pain management and associated postoperative inflammatory conditions.

1.2 Objectives

The objective of this systematic review was to systematically map and evaluate the available evidence on the safety and efficacy of diclofenac in managing postoperative pain following third molar surgery. Specifically, this review aims to:

1. Assess the effectiveness of diclofenac in reducing pain intensity and improving recovery outcomes after third molar removal.
2. Examine the safety profile of diclofenac, focusing on the incidence and severity of adverse effects.
3. Compare the efficacy and safety of diclofenac with other commonly used analgesics in the postoperative management of third molar surgery.
4. Identify knowledge gaps and suggest areas for future research regarding the use of diclofenac in this clinical context.

1.3 Research question

The research question was formulated whether the diclofenac shows higher efficacy and safety profile over the other NSAIDs in the management of postoperative pain after third molar surgery. The PICO structure of the research question was as follows:

Participants – Patients with symptomatic third molars

Intervention – Surgical extraction of third molars under local anesthesia

Comparison – Comparison with other NSAIDs and/or placebo

Outcomes – Efficacy of diclofenac over other NSAIDs

2. MATERIAL AND METHODS

2.1 Protocol and Registrations

The protocol of the present systematic review and meta-analysis was registered on PROSPERO international prospective of systematic reviews under registration number CRD420250651242 on 24th February 2025.

2.2 Eligibility criteria

The present systematic review followed the PRISMA guidelines for the assessment of the efficacy of diclofenac in managing postoperative sequelae after mandibular third molar extraction. The articles searched on the databases were sorted based on the following exclusion and inclusion criteria:

2.2.1 Inclusion Criteria:

1. Study Type: Randomized controlled trials / Clinical trials
2. Language: Articles published in English.
3. Population: Human studies on the adult population (age more than 18 years) undergoing third molar surgery.
4. Intervention: Studies in which diclofenac was administered orally or parenterally as the primary pharmacological intervention for postoperative pain management.

5. Outcome Measures: Efficacy (e.g., pain relief, anti-inflammatory effects) and safety (e.g., gastrointestinal, renal, and cardiovascular adverse effects), comparisons of diclofenac with other NSAIDs and placebo, and variable dosing forms of diclofenac.

2.2.2 Exclusion Criteria

1. Study design: Studies that used split-mouth design for comparison of various drugs.
2. Intervention: Studies where diclofenac was used in combination therapies without clear delineation of its specific effects.

2.3 Information sources

We conducted a deep search of PubMed/MEDLINE and EBSCOhost databases till 3rd March 2025. The periodic search was continued during the preparation of the manuscript so as to find any new publications across the databases.

2.4 Search strategy

The search terms "Diclofenac", "postoperative dental pain", and "third molar extraction or surgery" were used for article data retrieval under the search schema of "All fields" in the query box of the advanced search engine on PubMed/Medline and EBSCOhost. The Boolean operator provided for the search exhibited as ((diclofenac) AND (postoperative dental pain)) AND (third molar extraction or surgery)). Clinical trials were only included after using advanced filter. Articles published in English language only were screened for review.

2.5 Selection process

A total of 115 studies were retrieved after the deep search of the PubMed/Medline database and 152 studies were retrieved from EBSCOhost. Studies swotted by the authors for the content, search keywords and relevance for the present review. Initial scrutiny yielded 57 clinical trials / randomized controlled trials. Thus, 57 articles were analysed for content and relevant data to study the efficacy of diclofenac compared to other NSAIDs. Further, 33 articles were eliminated based on exclusion criteria. Finally, 24 research articles were presented for scoring and systematic review based on PRISMA guidelines (Figure 1).

2.6 Data collection process

The authors thoroughly revised the finalized 24 articles using the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for article selection that follow the protocol for case-control studies.[8] All these articles fulfilled the SIGN criteria and were tabulated for analysis, data screening and inferences. These potentially relevant studies were assessed individually by three authors for eligibility, and any disagreements were sorted by re-reading and resolving the conflicts.

2.7 Data items

The primary outcome data was retrieved for assessment of pain using visual analogue scale (VAS) at least 24 hours after the surgical removal of mandibular third molar. Other parameters like postoperative swelling, limitation in mouth opening and use of rescue analgesics were reviewed, however, the assimilated data was incoherent for the purpose of statistical analysis.

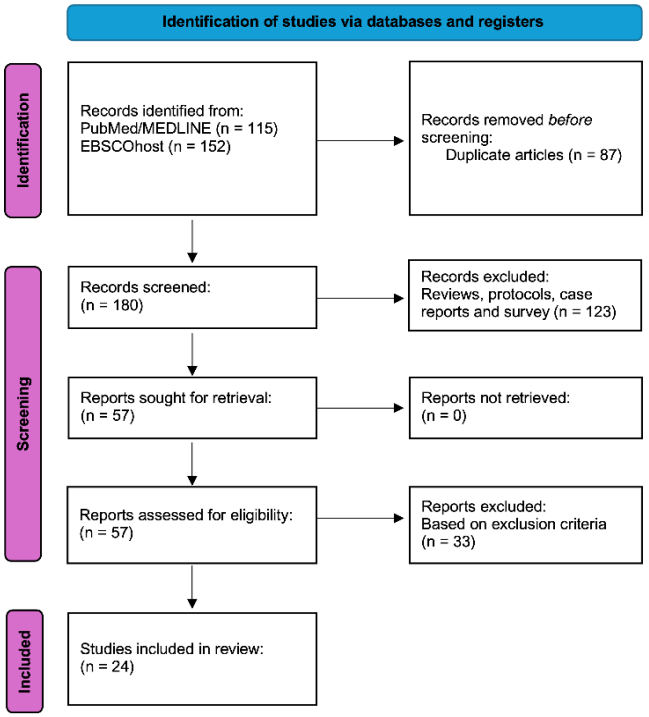

Figure 1. PRISMA Flow Diagram

2.8 Risk of biases assessment

The included articles for the review have Diclofenac as common variable while the comparison variables are different NSAIDs and placebo. Moreover, the observable biases included variations in visual analog scale and verbal rating scale scores. While few studies focused on total pain relief scores, the studies did not utilize the same standardized facial measurements for analysis of postoperative swelling. The presented data in the included studies was continuous and hence could not be analyzed by the COCHRANE Risk of Bias assessment tool.

2.9 Synthesis measures

Review manager computer program (RevMan) version 5.4 was used for data entry and calculation of effect size for VAS from six studies.[9]

The forest plot was derived by entry of VAS scores recorded for diclofenac against other NSAIDs used for comparison during third molar surgery. The qualitative syntheses for diclofenac were focused on efficacy, safety profile, effect on inflammatory mediators and other relevant findings.

3. RESULTS

3.1 Study selection

This systematic review synthesizes findings from 24 studies on the efficacy and safety profile of diclofenac in managing postoperative pain following third molar surgery. The included studies evaluated various formulations of diclofenac, including oral, injectable, transdermal, and submucosal forms, and compared them to other NSAIDs or placebo. Studies that were presented through the search engine but did not qualify in the systematic review were excluded based on the defined inclusion and exclusion criteria.

3.2 Study characteristics

The articles collected were randomized clinical/control trials, case-control, and comparative studies that fulfilled the inclusion criteria had relevance in synthesizing evidence were summarised for primary objectives and outcomes.

3.3 Results of individual studies

Efficacy of Diclofenac

Several studies have confirmed the effectiveness of diclofenac as a standalone analgesic for postoperative pain. Zuniga et al. found that liquid-filled diclofenac capsules significantly improved pain outcomes with a rapid onset of relief, observed within 30 minutes in their later study.[10,11] Similarly, Gorecki et al. reported that submucosal diclofenac effectively reduced pain following third molar surgery and required fewer rescue analgesics compared to placebo.[12]

Diclofenac was consistently found to be comparable to other analgesics in controlling postoperative pain. Orozco-Solís et al. compared 100 mg diclofenac to 15 mg meloxicam following third molar extraction and found no statistically significant differences in pain control, facial swelling, or trismus, indicating similar efficacy between the two drugs.[13] Similarly, Ahlstrom et al. found that diclofenac provided similar pain relief compared to ibuprofen (400 mg), with a comparable safety profile.[14] Shah et al. also highlighted diclofenac's superiority to placebo, showing a significant reduction in postoperative swelling and tenderness, further supporting its role in both analgesia and inflammation control.[15] Diclofenac was similarly effective across different formulations. Seymour et al. found that intravenous diclofenac in doses of 25, 50, and 75 mg provided comparable pain relief, indicating that the dose did not significantly affect the drug's efficacy.[16]

Hofele et al. found that both tablet and sachet forms of diclofenac provided effective pain management, though the sachet form offered incremental benefits in terms of analgesia.[17] Samal et al. compared the transdermal patch to oral and intramuscular diclofenac and concluded that transdermal and oral forms had similar analgesic efficacy however, the injectable form provided better pain control.[18] Diclofenac had similar efficacy to piroxicam but had a shorter duration of action and slightly lower incidence of nausea and vomiting as suggested by Wakeling et al when used as a suppository.[19] However, a study has shown a better analgesic effect, longer duration of action and fewer adverse events associated with the use of other NSAIDs tenoxicam.[20]

Safety Profile of Diclofenac

The safety profile of diclofenac has been generally favorable, with most studies reporting a tolerable adverse effect profile compared to other NSAIDs.

Common side effects of diclofenac included gastrointestinal discomfort, nausea, headaches, and dizziness, but these were generally mild and comparable to other NSAIDs. Joshi et al. found that diclofenac was associated with side effects such as nausea and gastrointestinal discomfort, but these were not significantly different from those observed with ibuprofen and paracetamol with codeine.[21] Manvelian et al. found that diclofenac (in both 18 mg and 35 mg doses) had high overall efficacy and tolerance, with treatment-related adverse effects being comparable to celecoxib.[22]

In comparative studies, diclofenac was generally found to have a safety profile similar to other NSAIDs, such as ketoprofen and ibuprofen. Tai et al. showed that diclofenac provided better pain relief than controlled-release ketoprofen, with similar adverse effects, further supporting diclofenac's favorable safety profile.[23] Gaetano et al. compared diclofenac with etoricoxib and found both drugs to be effective, though etoricoxib resulted in a statistically significant reduction in pain severity.[24] Mohammad et al. compared sublingual piroxicam with oral diclofenac (150 mg) and found that piroxicam demonstrated better tolerability and efficacy.[25] Shukla et al. also reported that piroxicam provided better analgesic properties and required fewer rescue analgesics compared to diclofenac, although other analgesics like tramadol and paracetamol were less effective.[26] MV et al. conducted a study comparing the intramuscular administration of ketoprofen and diclofenac for postoperative pain management. The results suggested that both drugs exhibited comparable efficacy in alleviating postoperative pain, leading the authors to propose that ketoprofen and diclofenac could be used interchangeably for this indication.[27]

Effect of Diclofenac on Inflammatory Mediators

Diclofenac's role in modulating inflammatory mediators, particularly its effects on C-reactive protein (CRP) levels and swelling, was investigated in several studies. Singh et al. compared diclofenac to mefenamic acid and found that both drugs were equally effective in pain relief, though mefenamic acid significantly reduced serum CRP levels compared to diclofenac.[28]

Salgia et al. also measured CRP levels and found that diclofenac caused the lowest increase in CRP among the NSAIDs tested, further suggesting that diclofenac may have a milder impact on systemic inflammation than some other NSAIDs like mefenamic acid.[29]

Effect of Diclofenac on other postoperative sequalae

Diclofenac's anti-inflammatory effects were also evident in reducing postoperative swelling and tenderness. Shah et al. found that diclofenac significantly reduced postoperative swelling and tenderness compared to placebo, indicating its efficacy in managing local inflammation.[15] Similarly, Orozco-Solís et al. found that diclofenac provided comparable effects to meloxicam in controlling facial swelling and trismus after third molar extraction, highlighting its role in managing both pain and inflammation.[13]

Kaplan et al. compared diclofenac to tenoxicam and flurbiprofen, noting that while tenoxicam was superior in terms of pain control, diclofenac was still effective and its anti-inflammatory properties were evident.[30] Additionally, Mony et al. assessed the preemptive analgesic effects of diclofenac and ketorolac, concluding that both medications significantly provided postoperative pain-free periods, suggesting that diclofenac's anti-inflammatory properties may contribute to its analgesic effects.[31]

Furthermore, a study highlighted the role of diclofenac in reducing inflammation, suggesting that only 30% of patients receiving diclofenac required rescue analgesics, suggesting good control over both pain and inflammation.[32]

Other relevant findings

Hersh et al. studied the dose-ranging of Prosorb diclofenac potassium (25, 50, and 100 mg) and found that all doses were more effective than placebo, with rapid onset and good tolerability, further supporting the efficacy of diclofenac in managing postoperative pain and inflammation.[33]

Results of syntheses

Six studies provided the relevant data for sample size and mean pain scores with standard deviations (SD).[25 – 27, 29, 31, 32]

The forest plot analysis was performed for these studies using RevMan for academics.[9]

The synthesis calculated the pooled average effect size, SD, at a 95% confidence interval (CI). The analysis revealed a nonsignificant comparison between pooled pain scores of diclofenac versus other NSAIDs (p-value = 0.82, effect size =0.03, and 95% CI range = -0.23 to 0.29). Forest Plot of pooled effect size, estimates and 95% confidence interval representing differences in VAS scores for the six studies (Figure 2).

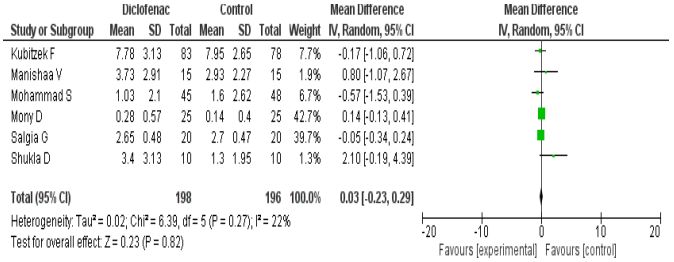

Figure 2. Forest Plot of pooled effect size, estimates and 95% confidence interval representing differences in VAS scores

3. DISCUSSION

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) belonging to the carboxylic acid class and is a phenylacetic acid derivative. It exerts its analgesic effects by inhibiting cyclooxygenase (COX) enzymes, key players in the arachidonic acid pathway responsible for prostaglandin synthesis. By blocking COX, diclofenac reduces the inflammation and pain that arise post-surgery, making it particularly effective in managing postoperative dental pain after oral procedures such as third molar extractions.[16] These surgeries offer a standardised model for evaluating analgesic efficacy due to their consistency and the availability of healthy individuals as study subjects. Numerous studies have demonstrated the efficacy of NSAIDs in alleviating dental pain, and diclofenac, a widely used agent in the field, has shown significant analgesic potential. However, its recommendation has waned recently, raising questions about its current standing in pain management protocols.[34] This systematic review includes 24 studies examining diclofenac's efficacy, tolerability, and safety in managing postoperative dental pain. The evidence consistently supports diclofenac as a highly effective analgesic for postoperative pain, particularly in dental and third molar surgeries. Its efficacy stems from inhibiting COX enzymes, reducing prostaglandin production, which mediates pain and inflammation. The findings reinforce diclofenac's continued relevance in pain management, with studies demonstrating its comparable or superior efficacy to other common analgesics, such as meloxicam, tramadol, ibuprofen, and paracetamol. In submucosal formulations, diclofenac demonstrated a faster onset and reduced need for rescue analgesics, improving patient comfort post-surgery.[12]

Additionally, when compared to other NSAIDs such as ibuprofen, ketoprofen, and piroxicam, diclofenac is shown to be at least comparable, if not superior, in terms of pain relief and rescue analgesic consumption. [26]

However, when compared to etoricoxib, a selective COX-2 inhibitor, diclofenac performed less favorably in certain cases. Etoricoxib may offer superior pain relief with potentially fewer gastrointestinal side effects due to its selective inhibition of COX-2, rather than the

non-selective COX inhibition seen with diclofenac. This suggests that newer COX-2 inhibitors may have a role in pain management with fewer adverse effects, particularly in patients with a higher risk of gastrointestinal irritation. This highlights the importance of personalized treatment based on patient characteristics and the clinical scenario.[24] Further studies comparing various delivery routes (oral, intravenous, submucosal) also indicate consistent efficacy across formulations. Another study found that intravenous diclofenac, regardless of the dose (25 mg, 50 mg, or 75 mg), provided comparable pain control.[16] Oral tablets and soft gel capsules also showed similar efficacy, with liquid-filled capsules offering a faster onset, beneficial for acute pain management.[10, 11]

Diclofenac also demonstrates its dual role in pain relief and inflammation modulation. Studies show that it reduces inflammatory markers like CRP more effectively than other NSAIDs, such as mefenamic acid, which is especially significant in postoperative care, where inflammation is a key factor in pain perception and healing.[28, 29] This may provide added advantages over other NSAIDs by reducing both pain and inflammatory sequelae more effectively.

4.1 Limitations and Future Directions

Despite diclofenac's effectiveness, several limitations must be considered. Many studies in this review had small sample sizes and primarily assessed short-term outcomes (e.g., pain within the first few days after surgery). These limitations hinder the ability to conclude the long-term safety and efficacy of diclofenac. Future studies should include larger sample sizes and evaluate long-term outcomes, particularly concerning gastrointestinal, renal, and cardiovascular effects—common concerns with prolonged NSAID use. Most studies in this review have not specified the type of trial in methodology.

Thus, also leading to issues with justification for selection of comparing drug.

Another limitation is that most studies did not assess inflammatory markers or other biomarkers of healing, even though inflammation plays a critical role in postoperative recovery. Future studies could benefit from including serum CRP levels or other inflammatory biomarkers to better understand diclofenac's impact on inflammation.

Moreover, the findings of this review primarily focus on third molar extractions, a standardized surgical procedure, which may not be fully applicable to other surgical types or more diverse patient populations.

Additionally, while diclofenac is widely used in clinical practice, the absence of head-to-head comparisons with newer COX-2 inhibitors or other non-opioid analgesics leaves its relative position in pain management protocols unclear. Future research could directly compare diclofenac with emerging agents to help establish clearer guidelines for postoperative pain management across a variety of surgical settings.

3. Summary and conclusion

This systematic review underscores the pivotal role of diclofenac as an effective NSAID in managing postoperative dental pain, particularly following third molar extractions. The synthesis of evidence from the selected studies reveals that diclofenac has comparable analgesic efficacy and demonstrates a favorable safety profile to other NSAIDs.

However, the review also highlights significant gaps in the current literature, particularly concerning the long-term effects of diclofenac in diverse patient populations and the need for standardized assessment criteria that incorporate inflammatory markers. While the majority of studies focus on short-term outcomes, the implications for chronic pain management remain underexplored. Furthermore, the findings are primarily relevant to adult patients undergoing third molar surgery, potentially limiting their applicability to broader surgical contexts or pediatric populations.

In conclusion, while diclofenac remains a cornerstone in the arsenal of postoperative pain management, continued research is essential to address the identified gaps and optimize its use across various clinical scenarios. The need of the hour is to develop standardized guidelines and protocol for selection of analgesics for specific outcome and the procedures and not merely relying on clinicians' experiences.

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Ethical Approval

Not applicable

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