

Intra-Carpal Injection of Ketorolac Compared with Triamcinolone for Carpal Tunnel Syndrome; A Randomized Controlled Trial

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Abstract

Introduction: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity that can be treated with surgical and non-surgical methods. Ketorolac, a nonsteroidal anti-inflammatory drug, is commonly used for musculoskeletal disorders, but its intra-carpal injection has not been studied. Therefore, we conducted a controlled trial to compare ketorolac with triamcinolone in CTS.

Methods: In this blinded, randomized, controlled trial, patients with mild to moderate CTS were randomly allocated to two treatment groups to receive either a local injection of 30 mg ketorolac or 40 mg triamcinolone. Patients were evaluated based on the Boston Carpal Tunnel Questionnaire, electrodiagnostic findings, patient satisfaction, and any injection site reactions.

Results: Finally 43 patients were completed the study according to the protocol. Both groups showed significant improvement in the visual analog scale (VAS) and Boston Questionnaire Symptom Severity Scale (BQ-SS), Boston Questionnaire Functional Status Scale (BQ-FS), and electrodiagnostic scores at 3 months were compared with the baseline ($P < 0.001$). Comparison of the groups showed significant differences with respect to VAS, BQ-FS, and BQ-SS, with the observed improvement being significantly higher in the triamcinolone group. There was no difference between the two groups regarding electrodiagnostic results, patient satisfaction, and injection complications.

Conclusions: This study shows that injection of triamcinolone or ketorolac in patients with mild to moderate CTS resulted in improvement of pain, function, and electrodiagnostic findings; it also revealed that triamcinolone was superior to ketorolac in providing better analgesic effect and resulted in greater improvement in symptom severity and function.

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity (1). It has a prevalence of 3.5–6.8% in the general population and is 3 to 10 times more common in women than in men (2). In this condition, the median nerve is compressed as it passes through the carpal tunnel (3). Clinical features of CTS include pain, burning, tingling, and paresthesia in the distribution of the median nerve distal to the wrist (4). If the condition is left untreated, irreversible changes in the median nerve gradually occur, leading to atrophy of the wrist and disability of the affected hand (5).

Various treatment methods have been presented in the literature for the management of CTS, and the application of these methods depends on the severity of the syndrome (6).

This condition can be treated either surgically or non-surgically (7). Classically, conservative therapies are the first line of treatment for mild to moderate CTS. Surgical intervention is recommended when mild to moderate CTS are refractory to therapy or severe sensory or motor impairment cases. Common non-surgical treatments include activity modification (e.g., restriction of wrist motion), wrist splints, physical modalities, exercise therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, pyridoxine, local injections of triamcinolone and progesterone (8,9).

Local injection of triamcinolone is one of the most commonly used measures for the conservative treatment of CTS with satisfactory short-term results (10). Despite the good short-term results, the long-term results are variable, and the effects are usually less remarkable in the long term (11). According to the study by Karadaş et al., local injection of triamcinolone significantly improves the diagnostic criteria of CTS, and this improvement persists up to six months after treatment (12). Local injection of triamcinolone is also associated with adverse effects, especially with repeated injections, including depigmentation and trauma to blood vessels and nerves, limiting this substance's use (9). Therefore, the introduction of other effective local injections for the treatment of CTS is still under discussion.

Ketorolac, an injectable NSAID, is commonly used for musculoskeletal pain syndromes (13). Local ketorolac injection achieves a higher concentration, resulting in better therapeutic effects and fewer systemic side effects such as gastrointestinal and renal problems (13,14). There are few studies on local ketorolac injection in musculoskeletal disorders (13,15). According to a 2011 study, patients with knee osteoarthritis (OA) who received hyaluronic acid (HA) experienced an earlier analgesic effect with the concomitant use of local ketorolac injection (13). Another 2015 study found that local ketorolac injection had a similar analgesic effect to triamcinolone in hip OA and could be used as an alternative in patients with steroid contraindications (15).

Because of the high prevalence of CTS and the paucity of studies on local ketorolac injection, we decided to compare the effect of local injection of ketorolac with that of triamcinolone in the treatment of patients with mild to moderate CTS.

Material & Methods

Design & Setting

The study was registered while recruiting patients on the Iranian Registry of Clinical Trials (IRCT) website <http://www.irct.ir/>, a WHO primary register setup, with registration number of IRCT20130523013442N29 on 13/09/2019. We conducted a randomized controlled trial with two 1:1 parallel arms from January 2019 to November 2020. The study was conducted in two outpatient physical medicine and rehabilitation clinics at Modares and Shohadaye Tajrish hospitals. Both are teaching hospitals of Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran, with a high patient volume.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the institutional research ethics committee of Shahid Beheshti University of Medical Sciences under reference number IR.SBMU.MSP.REC.1397.397. All participants signed their written informed consent. The trial investigator explained the objectives, benefits, and potential side effects of the trial to eligible patients. Patients were informed that they were free to withdraw from the study at any time before surgery.

Eligibility

We invited males or females aged >18 years with signs/symptoms of CTS to undergo an electrodiagnostic study. According to the electrodiagnostic criteria (16), patients with mild to moderate CTS, with pain intensity of ≥ 4 , were considered eligible. Exclusion criteria were: severe CTS requiring surgical intervention, polyneuropathy, cervical radiculopathy, thoracic outlet syndrome (TOS), local triamcinolone injections into the carpal tunnel or night splint in the past 6 months, carpal tunnel release surgery (CTR), allergic reactions to triamcinolone and NSAIDs, malignancy, skin infections at the injection site, and pregnancy.

Recruitment

Initially, patients with signs/symptoms of CTS were invited for a screening appointment. During the interview at the first visit, the study phases and reasons for participation were explained to all potential participants. When a patient declined to participate, another was selected and invited in the same manner until the required sample was recruited. At the screening visit, medical history and physical examination were obtained. Electrodiagnostic studies were then requested. Patients were asked about their medication history and dietary supplement use; their responses were recorded on case report forms that conformed to principles of good clinical practice. We reviewed the records, and patients were then presented to a consensus committee of the authors, who confirmed their eligibility and invited them to participate in the study. Participants who gave written informed consent were assigned to one of the study groups.

Interventions & Preparations

At the beginning of the study, participants were given both verbal and written information by a specialist in physical medicine and rehabilitation about the injections and their benefits and possible side effects. In both groups, the procedure involved an injection. In the ketorolac group, patients received 1 mL of 30 mg/mL ketorolac (Exir Company, Iran) and 0.5 mL lidocaine (2%, Caspian Company, Iran). In contrast, in the second group, the local injection was 1 mL of 40 mg/mL triamcinolone acetonide (Hexal Company AG, Germany) and 0.5 mL lidocaine.

Injection Technique

Patients in both groups received a local injection via proximal access by a single experienced physical medicine and rehabilitation specialist under ultrasound (US) guidance. Participants were placed in the supine position. The skin over the injection site of the affected wrist was thoroughly prepared with povidone-iodine 10%. Under US guidance, the injection was performed with a 23-gauge needle approximately 1.5 inches long. After identifying the palmaris longus tendon, the needle was inserted on the volar side of the wrist at an angle of 30-40° on the medial side of this tendon 1-2 cm proximal to the distal wrist crease. Figure 1 shows the injection technique under US guidance. All patients were prescribed a static wrist splint for 6 weeks at night (prefabricated CTS orthoses with a static volar splint to position the wrist in a 0-5° extension). In both groups, patients were sent home with written instructions. They were instructed to maintain relative rest for 24 hours. It was recommended that a cold compress be applied for 10 minutes three times daily. Patients were allowed to take acetaminophen 500 mg (without codeine) every 4-8 hours if the pain was not under control. Patients were not allowed to take other pain-relieving medications such as NSAIDs, supplements, or vitamins for one week after the injection. It was generally recommended that they continue to do low to moderate physical activity and gradually increase it at their own pace.

Outcome Measurements

The primary outcome of this study was the Boston Carpal Tunnel Questionnaire (BCTQ). The secondary outcomes were the visual analog scale (VAS), electrodiagnostic findings, patient satisfaction, and any complications of the injection.

Boston Carpal Tunnel Questionnaire (BCTQ)

The BCTQ is a patient-reported questionnaire commonly used in patients with CTS. It includes two subscales, the Boston Questionnaire Symptom Severity Scale (BQ-SS) [11 items with a five-point rating scale ("none" or "never" to "very severe" or "continuous")] and the Boston Questionnaire Functional Status Scale (BQ-FS) [8 items with a five-point scale corresponding to the difficulty of the required daily task ("no difficulty" to "cannot perform")]. The sum of the scores is reported for each subscale because a higher score indicates greater disability (17). Several authors have evaluated the validity and reliability of the Persian version of the BCTQ in recent years (18,19).

Visual Analog Scale (VAS)

The VAS assesses pain and ranges from 0 (no pain) to 10 (severe pain). Participants were asked to indicate the maximum pain they had felt in the past 2 days on the VAS ruler.

Electrodiagnostic Findings

The electrodiagnostic evaluation was performed with a Natus Synergy Ultrapro S100 device. The compound motor action potential (CMAP) and sensory nerve action potential (SNAP) of the median nerve were recorded using the techniques described by Dumitru and Amato [13]. Peak distal sensory latency (DSL), onset distal motor latency (DML), and baseline-to-peak SNAP and peak-to-peak CMAP amplitudes were reported for each subject. Any adverse effect of the interventions was registered.

CTS Grading

Based on Stevens' modified criteria [1], diagnosed CTS patients were classified as mild, moderate, or severe: mild CTS was defined as prolonged median DSL, moderate as prolonged DSL and DML, and severe as prolonged DSL and DML, with either an absent SNAP or a low-amplitude or absent thenar CMAP.

Patient Satisfaction with and Complications of the Injection

All patients were rated for complications such as stiffness, heaviness, pain, and their treatment satisfaction on a 5-point Likert scale: 1) very dissatisfied, 2) dissatisfied, 3) neutral, 4) satisfied, and 5) very satisfied.

Follow-ups

In this study, the participants were assessed twice: before the intervention and 3 months after the injection. The instruments used were the BSTQ, VAS questionnaire, and electrodiagnostic evaluation.

Sample Size

In one study, Gurcay et al. compared the efficacy of local injection of 6 mg betamethasone in CTS with oral intake of 15 mg/day meloxicam for 3 weeks (20). They divided 32 participants into two groups: 18 patients in the steroid group and 14 in the NSAID group. They measured the functional status scale (FSS) 3 months after the intervention. Their results showed that the two groups were similar in FSS at the baseline. However, after 3 months, there was no significant difference between the oral NSAID group and the local steroid injection group in the mean FSS; $P > 0.05$. However, using the graphical data with the online Web plot digitizer (21) showed that the improvement percentage was 31.5% in the steroid group and 23.8% in the NSAID group. Given this difference, we needed 22 participants in each group to detect a significant discrepancy in the BCTQ for disability between our two groups at 3 months, a power of 80%, and a two-tailed P value of 0.05 as statistically significant. We added three additional participants to each group to ensure that the study would be sufficiently powered even if 10% of the participants were lost. Thus, a total of 50 participants were assigned to the study groups.

Randomization & Blinding

We used the block randomization method to randomly assign participants to two groups with the same size of 25 participants (50 patients in total). Random numbers were generated in an independent statistical room. The assignment sequence was concealed from all investigators and participants with sequentially numbered sealed envelopes containing cards with the allocation group. Opening of the envelopes, preparation of the injection solutions, and injection were performed by a nurse and an experienced physician who were not involved in the intervention or assessments. Because ketorolac is a clear solution and triamcinolone is a milky suspension, the filled syringes were wrapped with tape to ensure blindness so that the contents of the syringe could not be seen by the patient. Blinded investigators performed all follow-up examinations.

Statistical Analyses

The collected data were stored in the profile of each patient and analyzed using SPSS 24. The Shapiro-Wilk test was used to assess data distribution. Mean and standard deviation were used for quantitative variables, and relative frequency was used for qualitative variables. The t-test was used to compare normally distributed variables, and the Mann-Whitney U test was used when the distribution was not normal. Qualitative data were analyzed using the chi-square test. The level of significance was set at less than 0.05 in this study.

Results

A total of 50 patients were included in the study according to the inclusion and exclusion criteria. In the final phase of the study, 5 patients were excluded because of their COVID-19 infection, and 2 patients were lost during follow-up. Thus, the analysis was performed with 43 participants. Figure 2 details the consolidated standards for reporting trials (CONSORT).

Of the 43 patients, 10 were male (23.2%), and 33 were female (76.8%). There was no significant difference between the two groups in demographic variables, pain duration, severity of CTS symptoms, VAS, BCTQ, and electrodiagnostic examinations of CTS before the study ($P > 0.05$) (Table 1).

Table 1
Participants' demographics and baseline characteristic

Characteristic	Ketorolac (<i>n</i> = 21)	Triamcinolone (<i>n</i> = 22)	P- value
Baseline Characteristics			
Age (y), Mean ± SD	50.71 ± 9.92	53.05 ± 6.80	0.372
Sex (Male/Female)	4/17	6/16	0.721
Pain Duration (month), Mean ± SD	16.62 ± 0.43	16.23 ± 0.57	0.590
CTS severity (Mild/Moderate)	13/8	15/7	0.755
Outcome Measures (Mean ± SD)			
VAS	5.86 ± 2.29	5.27 ± 2.29	0.408
BQ-SS	32.05 ± 9.87	30.27 ± 9.49	0.551
BQ-FS	19.19 ± 6.69	21.86 ± 7.08	0.211
DSL	4.24 ± 0.55	4.36 ± 0.91	0.604
DML	4.39 ± 0.61	4.44 ± 0.85	0.824
Sensory Amplitude (μV)	27.70 ± 11.19	25.95 ± 9.70	0.586
Motor Amplitude (mV)	6.51 ± 1.34	6.66 ± 1.54	0.729

The course of outcome measurements in both treatment groups is shown in Table 2.

Table 2
The course of outcome measurements

Outcome Mean ± SD	Before intervention	After intervention	Mean Difference (95% CI)		P-value**
			Values	P-value*	
Visual Analog Scale					
Ketorolac	5.86 ± 2.29	3.71 ± 2.10	2.14 (1.56–2.72)	< 0.001	0.022
Triamcinolone	5.27 ± 2.29	2.09 ± 1.15	3.18 (2.49–3.88)	< 0.001	
Boston Carpal Tunnel Questionnaire					
Boston Questionnaire Symptom Severity Scale					
Ketorolac	32.05 ± 9.87	22.67 ± 9.93	9.38 (5.40–13.36)	< 0.001	0.032
Triamcinolone	30.27 ± 9.49	15.64 ± 5.73	14.64 (11.68–17.60)	< 0.001	
Boston Questionnaire Functional Status Scale					
Ketorolac	19.19 ± 6.90	13.48 ± 4.76	5.71 (3.35–8.08)	< 0.001	0.039
Triamcinolone	21.86 ± 7.08	12.77 ± 4.65	9.09 (6.79–11.39)	< 0.001	
Electrodiagnostic Studies					
Distal Sensory Latency Peak					
Ketorolac	4.24 ± 0.55	3.98 ± 0.50	0.26 (0.17–0.35)	< 0.001	0.793
Triamcinolone	4.36 ± 0.91	4.08 ± 0.65	0.28 (0.13–0.44)	0.001	
Distal Motor Latency Onset					
Ketorolac	4.39 ± 0.61	4.14 ± 0.65	0.25 (0.13–0.37)	< 0.001	0.873
Triamcinolone	4.44 ± 0.85	4.20 ± 0.71	0.24 (0.12–0.35)	< 0.001	
Sensory Amplitude					
Ketorolac	27.70 ± 11.19	33.49 ± 11.62	-5.79 (-9.10 – -2.47)	0.002	0.843
Triamcinolone	25.95 ± 9.70	32.15 ± 11.85	-6.20 (-8.93 – -3.46)	< 0.001	
Motor Amplitude					
Ketorolac	6.51 ± 1.34	7.20 ± 1.31	-0.69 (-0.97 – -0.40)	< 0.001	0.331
Triamcinolone	6.66 ± 1.54	7.59 ± 2.03	-0.93 (-1.35 – -0.51)	< 0.001	
* Comparing the mean difference within groups					
** Comparing the mean difference between groups					

In both groups, VAS, BQ-SS, BQ-FS, DSL, DML, and sensory and motor amplitudes improved significantly 3 months after the intervention (all with P-value < 0.01). The observed improvement in the subjective outcomes of the study, i.e., VAS, BQ-FS, and BQ-SS, was significantly greater in the triamcinolone group (VAS: mean difference (MD) = 2.14 in the ketorolac group vs. 3.18 in the triamcinolone group, df = 41, F = 0.68, P = 0.022; BQ-SS: MD = 9.38 in the ketorolac group vs. 14.64 in the triamcinolone group, df = 41, F = 2.24, P = 0.032; BQ-FS: MD = 5.71 in the ketorolac group vs. 9.09 in the triamcinolone group, df = 41, F = 0.56, P = 0.039). No difference was observed in electrodiagnostic results between the two groups (DSL: MD = 0.26

in the ketorolac group vs. 0.28 in the triamcinolone group, $df = 32.73$, $F = 6.75$, $P = 0.793$; DML: MD = 0.25 in the ketorolac group vs. 0.24 in the triamcinolone group, $df = 41$, $F = 0.28$, $P = 0.873$; sensory amplitude: MD = -5.79 in the ketorolac group vs. -6.20 in the triamcinolone group, $df = 41$, $F = 0.41$, $P = 0.843$, motor amplitude: MD = -0.69 in the ketorolac group vs. -0.93 in the triamcinolone group, $df = 41$, $F = 0.16$, $P = 0.331$).

Ketorolac injection was associated with a 36.5% improvement in patient-reported pain 3 months after treatment (based on the VAS), whereas the VAS improvement rate in the triamcinolone group was 60.3%. After ketorolac injection, a 29.3% improvement in symptom severity (based on the BQ-SS) and a 29.8% improvement in functional status (based on the BQ-FS) were observed, whereas in the triamcinolone group, the improvement rates were 48.4% and 41.6%, respectively.

Regarding post-injection complications, 7 patients from both groups experienced complications such as warm sensation, stiffness, and heaviness at the injection site. No significant difference was found between the two groups ($P = 0.873$). Regarding patient satisfaction after injection, of the 43 participants, 29 (67.4%) were either satisfied or very satisfied with the procedure. There was no significant difference in patient satisfaction between groups ($P = 0.826$). Table 3 shows the results on the complications of the injections and patient satisfaction after the injections in more detail.

Table 3
Complications of the injections and patient satisfaction with the injections in each group

Item		Ketorolac ($n = 21$)	Triamcinolone ($n = 22$)	P-value
Complication	No Complication # (%)	17 (80.9)	19 (86.4)	0.873
	Warm sensation # (%)	1 (4.7)	2 (9.1)	
	Stiffness & Heaviness # (%)	3 (14.3)	1 (4.5)	
	Injection Site Pain (Mean \pm SD)	1.68 \pm 0.92	1.50 \pm 2.22	
Satisfaction # (%)	Very Dissatisfied	1 (4.7)	0 (0)	0.826
	Dissatisfied	1 (4.7)	1 (4.5)	
	Neutral	6 (28.5)	5 (22.7)	
	Satisfied	8 (38.1)	9 (40.9)	
	Very Satisfied	5 (23.8)	7 (31.8)	

Discussion

Classically, conservative therapies are the first choice for mild to moderate CTS. Surgical intervention is recommended in severe cases with severe sensory or motor impairment or resistance to conservative treatments (6,7). NSAIDs are one of the conservative treatments described in the literature to treat mild to moderate CTS. In most studies, NSAIDs have been used as an oral treatment or during phonophoresis (11,22–24). Based on several systematic reviews, oral NSAIDs have not shown significant benefit and are therefore not recommended as part of the routine CTS treatment algorithm (22). According to the American Academy of Orthopedic Surgeons (AAOS) guideline, oral NSAIDs have no added benefit compared with placebo (23). Local injection of NSAIDs results in high concentrations of these agents at the site of injury, which may result in greater efficacy and fewer systemic side effects (25). However, safety is a major concern with the local injection of NSAIDs. Koh et al. (26) studied the efficacy and safety of intra-articular ketorolac for OA of the first carpometacarpal joint (CMCJ). In their study, US-guided intraarticular injection of 0.5 mL of hyaluronic acid and 0.5 mL of 30 mg/mL ketorolac resulted in significantly faster pain relief than hyaluronic acid alone. Ahn et al. also showed that US-guided intraarticular ketorolac injection successfully improved pain and functional status in patients with adhesive

capsulitis, similar to corticosteroid injection. In addition, the improvement in shoulder ROM was greater in patients who received ketorolac (27).

This study indicates that ketorolac injection into the carpal tunnel is safe and causes no apparent complications. The incidence of injection complications was not significantly different between the two groups.

To our knowledge, the present randomized controlled trial is the first study to investigate the role of local ketorolac injection in CTS. Although the within-group analysis showed a significant improvement in the VAS, BQ-FS, BQ-SS, and electrodiagnostic findings, 3 months after the intervention, the between-group analysis showed the improvement in subjective outcomes, i.e., the VAS, BQ-FS, and BQ-SS, was lower in patients receiving ketorolac. Evaluation of the electrodiagnostic findings showed that although a greater mean difference was observed in the triamcinolone group, the difference between the two groups was not significant.

Some limitations should be considered when interpreting the results. The main limitations of this study were the limited follow-up period (3 months) and small sample size. The sample was also lacked a negative control, which means no one used a splint as a comparison. A wrist splint is often recommended for a better understanding of the role of ketorolac in the treatment of CTS.

Conclusion

According to the present study results, injection of triamcinolone or ketorolac into the carpal tunnel was associated with improvement in pain, function, and electrodiagnostic findings in patients with mild and moderate CTS. Triamcinolone was superior to ketorolac with a better analgesic effect and greater improvement in symptom severity and function. Evaluation of the incidence of injection complications also showed that injection of ketorolac into the carpal tunnel was safe and tolerable, with no significant difference from triamcinolone.

Abbreviations

AAOS	American academy of orthopedic surgeons
BCTQ	Boston carpal tunnel questionnaire
BQ-FS	Boston questionnaire functional status scale
BQ-SS	Boston questionnaire symptom severity scale
CMAP	compound motor action potential
CMCJ	carpometacarpal joint
CONSORT	consolidated standards of reporting trials
COVID-19	coronavirus disease of 2019
CTR	carpal tunnel release
CTS	carpal tunnel syndrome
DML	onset distal motor latency
DSL	peak distal sensory latency
IRCT	Iranian registry of clinical trials
MD	Mean Difference
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
SBMU	Shahid Beheshti University of Medical Sciences
SNAP	sensory nerve action potential
SPSS	statistical package for the social sciences
TOS	thoracic outlet syndrome
US	ultrasound
VAS	visual analogue scale

Declarations

Ethics Approval & Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the institutional review board of SBMU under reference number IRCT20130523013442N29. All participants signed their written informed consent. The trial investigator explained the objectives, benefits, and potential side effects of the trial to eligible patients. Patients were informed that they were free to withdraw from the study at any time before surgery.

Consent for Publication

Not Applicable.

Availability of Data & Materials

The datasets used and analysed during the current study are available on <https://reshare.ukdataservice.ac.uk/cgi/users/home?screen=EPrint::Summary&eprintid=855732>.

Competing Interests

The authors declared no potential conflicts of interest related to the research, authorship, and/or publication of this article.

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Authors' Contributions

AK, SHA and HE contributed to the design and development of the study protocols. AK performed the injections. NB, SHA and ME contributed to the eligibility decision. HE conceived and designed the study, guided protocol development, and helped with literature review and interpretation of the results. HE, AK, and NB developed the study protocols and conducted statistical analyses. AK, ME, SHA, and NB led the recruitment process, interviewed the patients, and performed the physical examinations and outcome measurements. All authors were involved in drafting the study and its final approval.

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Figures



Figure 1

The injection technique under ultrasound (US) guidance

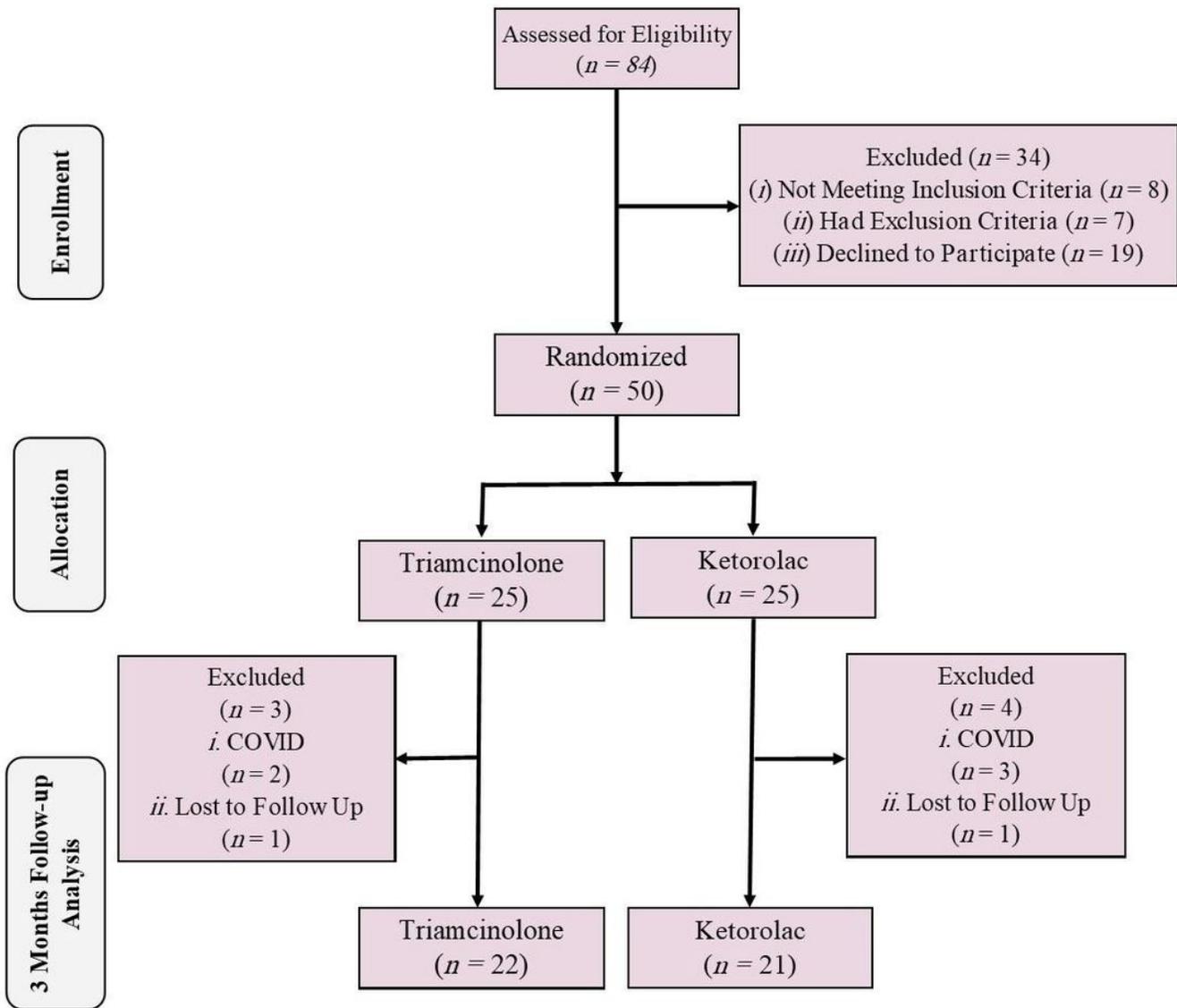


Figure 2

The Consolidated Standards for Reporting Trials (CONSORT) Flow Diagram