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Intracarpal midazolam: does it offer better pain relief than dexamethasone in carpal tunnel syndrome patients? A randomized double-blind clinical trial

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ABSTRACT

Background: Intracarpal injection of steroids has produced favorable effects in patients with carpal tunnel syndrome (CTS); however, it still carries some drawbacks. Perineural midazolam injection has some promising effects in chronic neuralgia. This study focused upon pain visual analog scale (VAS) improvement, and Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) improvements when comparing intracarpal injection of midazolam versus dexamethasone.

Methods: One hundred and thirty-four patients with mild to moderate CTS were randomized (1:1 ratio) to receive intracarpal 3 ml bupivacaine 0.5% with either 8 mg dexamethasone in 2 ml saline (group DX) or 2 mg midazolam in 2 ml saline (group MZ). VAS and BCTQ were assessed preintervention and postintervention (1st week, 1st, 3rd, and 6th months)

Results: The VAS showed a significantly lower value in MZ than the DX group with median value of 2 (maximum-minimum = 1–3) in MZ and 4 (2–5) in DX by the 6th month $p = 0.049$. Intragroup comparison of follow-up VAS to the baseline value showed significant decreases in the MZ group during the whole study period, whereas in DX the decrease was noticed by the 1st week and 1st month only. In postinterventional BCTQ, both symptom severity (SSS) and functional severity (FSS) scores were significantly lower in MZ rather than DX group after the 1st, 3rd, and 6thmonths where SSS ($p = 0.029$, 0.048, 0.04) and FSS ($p = 0.04$, 0.019, 0.003) in consequence.

Conclusions: Intracarpal injection of midazolam offers a longer duration of pain relief and higher hand functional improvement scores in comparison to dexamethasone.

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1. Introduction

Carpal tunnel syndrome (CTS) is one of the most common peripheral nerve entrapment problems of the upper extremity which is caused by compression of the median nerve through the carpal tunnel with a prevalence of 2%–3%

[1]. Increased mechanical pressure in the carpal tunnel can result in compression, inflammation, decreased blood supply, and damage of the median nerve [2]. Management of CTS may be carpal tunnel decompression for severe, prolonged, or conservative treatment irresponsive cases. Conservative may include splinting, physiotherapy, oral medications, and local injections. The mechanism of a local corticosteroid injection is suppression of inflammation and anti-edematous action, subsequently, decompression of the median nerve [3,4]. Despite the evident rapid onset of symptoms improvements with local steroid injection, lack of long-term effect and the undesirable effects, such as atrophy of the median nerve (MN), subcutaneous fat, and systematic complications have been reported [5,6].

On the other hand, midazolam, which is a short-acting benzodiazepine could possess its analgesic effects through gamma-aminobutyric acid (GABA-A) receptors stimulation found on the peripheral nerve [7,8]. Midazolam also was found to reduce C-fiber evoked activity. Kontinen and Dickenson in an animal study described that administration of midazolam 0.1–3.0 mg/kg subcutaneously reduced the A delta-fiber evoked activity in all studied groups, but the C-fiber evoked activity was reduced significantly only in the spinal nerve ligation group where neuropathic pain has been induced [9].

Accordingly, we have built the hypothesis to evaluate the value of ultrasonographic guided intracarpal midazolam injection in comparison to dexamethasone in patients with CTS over a period of 6 months follow-up. The primary outcome was to assess the change in

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pain visual analog scale (VAS). Secondary goals included assessment of changes in the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) [10] and improvement in the median nerve (MN) conduction study.

2. Materials and methods

This study was planned to be a randomized double-blind clinical trial. First, the protocol was approved by the local ethics committee (IRB644-4/2020) then registered at ClinicalTrials.gov (NCT04527770). The study was adhered to the declaration of Helsinki [11] and carried out following the CONSORT Statement. Participants were enrolled and followed up in pain clinic and electrodiagnosis units of anesthesia and rheumatology and rehabilitation departments in Faculties of medicine of Assiut, Minia and Fayoum universities. Written informed consent was obtained from each patient after the declaration of research benefits and possible side effects.

All patients' initial assessment was based upon the American Academy of Orthopedic Surgeons Clinical Practice Guideline [12] before their inclusion. The recruited participants have CTS of ≥6 months duration and a nonresponsive course to conservative therapy (nonsteroidal anti-inflammatory analgesics and night splint with vitamin B complex). Exclusion criteria included severe CTS (abductor policies brevis muscle atrophy with distal latency time >6.5 ms), MN electrophysiology study revealing absent potentials or its cross-sectional area (CSA) >15 mm^2 by sonographic checkup [13], previous surgery of carpal tunnel or CTS due to systemic causes, for example, endocrinal and/or pregnancy, rheumatoid arthritis, gouty or psoriatic osteoarthritis, concurrent use of antihistaminic, or cortisone. Participant refusal, local infection, presence of coagulopathy, and/or allergy to the included medications were also points for patients' exclusion from the study.

Before any intervention, baseline clinical and laboratory information were obtained from all patients. Symptoms of CTS, such as duration, laterality, pain and its radiation, paresthesia or numbness, weakness nocturnal awakening because of pain or tingling, clumsiness of the hand, were obtained. Pre-interventional laboratory investigations including international normalized ratio and platelet count were obtained.

The selected 134 patients were randomly allocated through a web-based randomizer in 1:1 ratio into two groups; **Group DX** received an intracarpal injection of 3 mL plain bupivacaine 0.5% and 2 mL of saline containing 8 mg dexamethasone, whereas **Group MZ** was injected with 3 mL plain bupivacaine 0.5% and 2 mg midazolam in 2 ml saline. The participant and outcome assessing physician were kept blind to the group implementation.

2.1. Ultrasound-guided MN evaluation and Hydrodissection injection Technique

The Patient was imaged under ultrasonography (U/S) while sitting with the shoulder in the neutral position and the forearm supinated. The forearm was placed on a custom-made table with the wrist in a neutral position. An ultrasound scanner (MyLab 7, Esaote, Europe B.V. Maastricht, Netherlands) 10-19 MHz high-frequency linear transducer, and a dedicated protocol with optimization of scanning parameters were used. The depth of the ultrasound image was adjusted to be 30 mm. The image acquisition frame rate was set to 60 Hz with minimal image compression.

Ultrasonographic evaluation of MN was attained at the distal wrist crease (DWC). Median nerve CSA and its characteristics regarding echogenicity, mobility, and vascularity were evaluated. Echogenicity score (ES) was assessed subjectively and rated as (normal = 2), (slightly decreased = 1), or (decreased = 0) based on visual inspection of the image, with normal nerve echogenicity showing a honeycomb pattern with a mixture of dark fascicles interspersed among a brighter background. To assess MN mobility, the participant was asked to repeatedly flex and extend the fingers and wrist while the transducer was kept over the DWC. Mobility score (MS) was also rated as (normal = 2), (slightly decreased = 1), or (decreased = 0). Normal mobility was seen when the MN sinks deeper to the flexor tendons during finger and wrist flexion. Vascularity score (VS) was assessed by placing the power doppler box over the MN and slowly increasing the gain. If the color flow was seen in the nerve before other structures (particularly the flexor tendons) then vascularity was rated as either (increased = 2) or (slightly increased = 1) based on the degree of color flow, and (normal = 0) when there was no early color Doppler signal in the nerve compared with the surrounding structures [14–16].

Under complete sterilization, a 26-gauge needle was inserted at the proximal wrist crease, just ulnar to the palmaris longus tendon, at a 30° angle to the skin and directed towards the index finger. Then, 3 mL of the study solution was injected through the in-plane ulnar approach, to detach the MN from the transverse carpal ligament, and an additional 2 mL was injected to separate the MN from the underlying flexor tendons [17].

2.2. Data collection

Pain VAS [18] and BCTQ were assessed pre-interventional. The BCTQ is a patient-based questionnaire and encompasses two components:

Symptom Severity Scale (SSS) and Functional Status Scale (FSS). The subscales score from 1 to 5, with higher scores indicating a greater degree of disability. The VAS and BCTQ were then evaluated post-interventional by the end of 1st week, 1st, 3rd, and 6th months. Any complication related to the procedure was recorded. Sonographic and electrophysiologic MN evaluations were established peri-interventional then postinterventional by the end of 1st, 3rd, and 6th months.

2.3. Statistical analysis

Before the study runover, the number of patients required in each group was determined according to data obtained by a pilot study performed on 20 consented candidates, 10 in each group. Based upon the assumed primary outcome assessment (to decrease VAS at least by 20%), a sample size of 130 patients was determined to provide 85% power at the level of 5% significance using G Power 3.1 9.2 software (UCLA, Los Angeles, California, USA). Accordingly, we included 134 patients for compensation of any dropout. Data distribution was firstly checked through Shapiro–Wilk test. Data are expressed as mean± standard deviation, ratio, number (percentage), and/or median (minimum-maximum) as appropriate. The Chi-square test was used for categorical data analysis. The statistical difference between the groups was compared using the independent Student's t-test for parametric continuous data and the Mann Whitney-U test for nonparametric continuous data. Intragroup data at different follow-up time points were compared to the baseline value using paired Student's t-test or Kruskal Wallis test as appropriate. All statistical tests were two-tailed, with $P < 0.05$ being considered statistically significant. SPSS version 22 (IBM Corp., Armonk, New York, USA) was used for statistical analysis.

3. Results

This study included 134 participants; they were evaluated and completed the study as shown in the CONSORT diagram (Figure 1). Patients in the two groups were comparable regarding their demographic and data (Table 1).

The VAS was significantly lower in the midazolam group than the dexamethasone group by the 6th month only. At the same time, a comparison of the follow-up results to the baseline values within each group revealed a significant decrease of the VAS in the MZ group during the whole study period, whereas in the DX group the VAS was significantly decreased by the 1st week and 1st month, then significantly increased in the 6th-month reading (Table 2).

Boston questionnaire score showed significant decrease in midazolam group compared to dexamethasone group. The SSS and FSS were

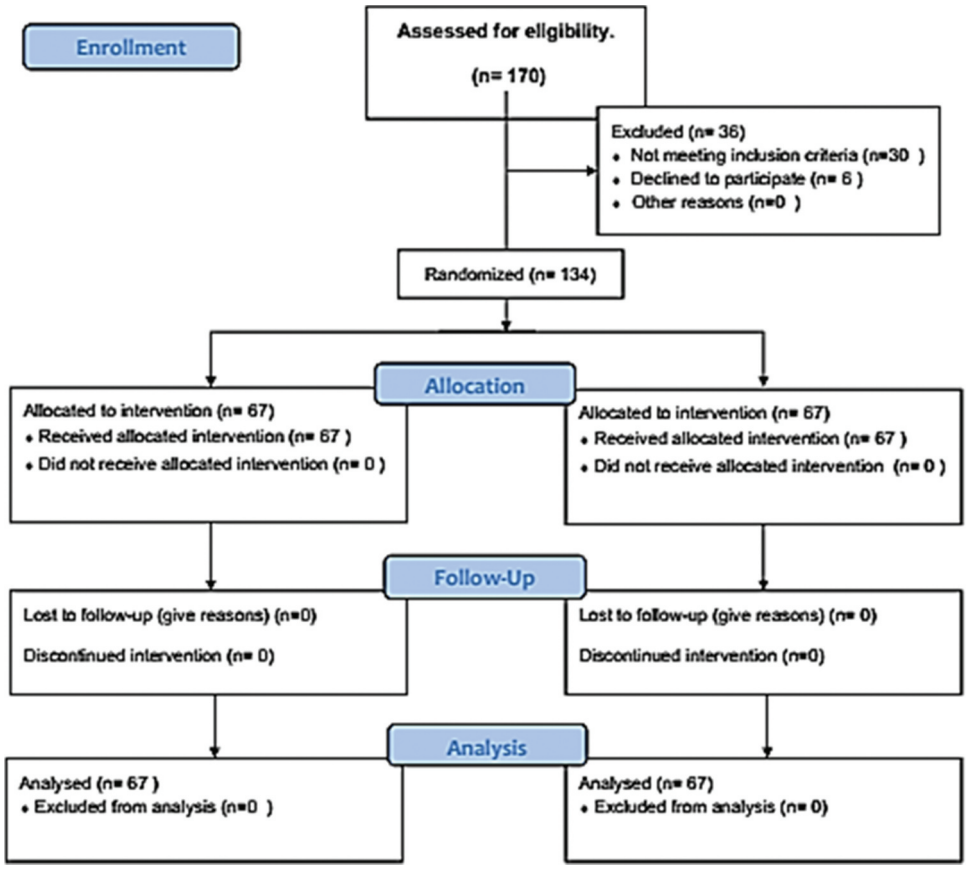

Figure 1. CONSORT flow chart of the participants.

Table 1. Demographic and clinical data of the studied groups.

Variables	Group DX n = 67	Group MZ n = 67	*P*
Age (years)	42.18 ± 10.2	44.76 ± 8.5	0.45
Male/Female	32/35	27/40	0.42
Height (cm)	167.11 ± 12.3	174.7 ± 3.5	0.51
Weight (Kg)	75.5 ± 8.2	77 ± 4.33	0.62
Duration (months)	8. 8 ± 2.5	8.6 ± 2.1	0.92
Paresthesia	67 (100%)	67(100%)	0.89
Nocturnal awakening	61 (91%)	59(89%)	0.6
Hypoesthesia	32(47.7%)	35(52.2%)	
Positive Hoffman Tinel Sign	33(49.2%)	35(52.2%)	0.88
Positive Phalen sign	49(73.13%)	47(70.1%)	0.9

Data are expressed as mean± standard deviation, ratio, number-(percentage). **DX** dexamethasone group, **MZ** midazolam group. $P < 0.05$ is considered statistical significance.

Table 2. Visual analog scale of the studied groups.

Variables	Group DX n = 67	Group MZ n = 67	*P*
Pre-injection	3(2–4)	4(2–5)	0.9
VAS 1st w	1(1–2) *	1(1–2) *	-
VAS 1st m	2(1–3) *	1(1–2) *	0.9
VAS 3rd m	3(2–4)	2(1–3) *	0.1
VAS 6th m	4(2–5) *	2(1–3) *	0.049

Data are expressed median (maximum-minimum). **DX** dexamethasone group, **MZ** midazolam group, **VAS** visual analog scale. (*) significant difference to the base line value. $P < 0.05$ is considered statistical significance.

significantly lower in the midazolam group in the 1st,3rd, and 6th months. Within each group, improvement of FSS and SSS was evident as a significant decrease in comparison to the baseline value starting from the 1st week and during the whole study period in the MZ group. In the dexamethasone group, both the SSS and FSS significant decrease was noted in the 1st week, 1st, and 3rd months only (Table 3).

The CSA was significantly lower in the MZ group than the DX group by the end of 1st, 3rd, and 6th months. The CSA showed a significant decrease in comparison to the pre-injection CSA during the whole study period in both groups, except in the 6th month's measure of the dexamethasone group (Figure 2).

Regarding to sonographic findings (Table 4), the ES and MS were significantly higher in the midazolam group than the dexamethasone group during the whole study period and significantly increased within each group in comparison to the basal reading in both groups, except in the 6th month's evaluation of the dexamethasone group. The VS showed a significant decrease in the midazolam group in comparison to the dexamethasone group during the whole study follow-up. At the same time, the VS was significantly decreased within each group in comparison to the basal reading in all patients, except in the 6th month's reading of the dexamethasone group.

Table 3. Boston Questionnaire of the studied groups.

	Group DX n = 67		Group MZ n = 67		*P*	P
Variables	SSS	FSS	SSS	FSS	SSS	FSS
Pre-injection	2.6 ± 0.1	2.7 ± 0.3	2.6 ± 0.3	2.5 ± 0.4	0.54	0.13
1st w	2.0 ± 0.03*	1.9 ± 0.3*	1.9 ± 0.5*	2.1 ± 0.1*	0.44	0.34
1st m	1.8 ± 0.2*	1.8 ± 0.1*	1.4 ± 0.5*	1.2 ± 0.3*	0.029	0.04
3rd m	1.8 ± 0.3*	1.7 ± 0.3*	1.3 ± 0.1*	1.3 ± 0.3*	0.048	0.019
6th m	2.7 ± 0.5	2.6 ± 0.3	1.6 ± 0.5*	1.7 ± 0.4*	0.04	0.033

Data are expressed as mean± standard error. **SSS** Symptom Severity Scale, **FSS** Functional Status Scale, **DX** dexamethasone group, **MZ** midazolam group, **VAS** visual analog scale. (*) significant difference to the base line value. $P < 0.05$ is considered statistical significance.

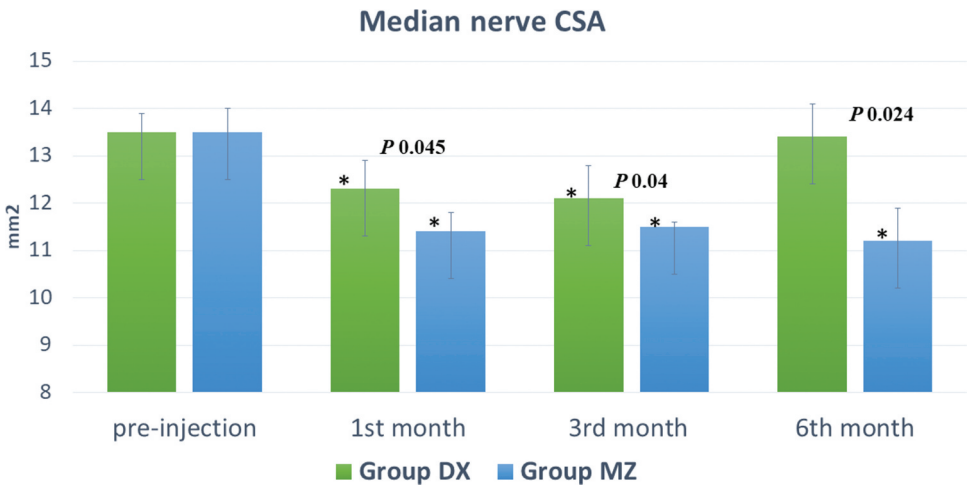

Figure 2. Median nerve cross sectional area in the two study groups. **Notes**: Data are expressed mean± standard deviation. **DX** dexamethasone group, **MZ** midazolam group, CSA cross-sectional area. (*) significant difference with the baseline value. $P < 0.05$ is considered statistical significance.

Table 4. Median nerve sonographic evaluation of the studied groups.

	E		M		VS	
Variables	DX	MZ	DX	MZ	DX	MZ
Baseline	1.4 ± 0.3	1.5 ± 0.2	1.2 ± 0.2	1.3 ± 0.4	1.7 ± 0.5	1.9 ± 0.7
	$P = 0.8$		$P = 0.4$		$P = 0.29$	
1st m	1.6 ± 0.5*	1.6 ± 0.7*	1.4 ± 0.6*	1.7 ± 0.8*	1.2 ± 0.3*	0.8 ± 0.3*
	$P = 0.04$		$P = 0.02$		$P = 0.01$	
3rd m	1.6 ± 0.9*	1.9 ± 0.1*	1.5 ± 0.9*	1.9 ± 0.2*	1 ± 0.9*	0.8 ± 0.5*
	$P = 0.04$		$P = 0.05$		$P = 0.03$	
6th m	1.5 ± 0.6	2 ± 0.2*	1.2 ± 0.2	1.8 ± 0.3*	1.6 ± 0.8	0.7 ± 0.1*
	$P = 0.04$		$P = 0.04$		$P = 0.03$	

Data are expressed mean± standard deviation. **ES** Echogenicity score, **MS** Mobility score, **VS** Vascularity score, **DX** dexamethasone group, **MZ** midazolam group. *P*-value between groups; P^1(ES), P^2(MS), P^3 (VS). (*) significant difference to the base line value. $P < 0.05$ is considered statistical significance.

Table 5. Median nerve electrophysiologic evaluation of the studied groups.

	SNCV		DML		*P*	*P*
Variables	DX	MZ	DX	MZ	*SNCV*	*MDL*
Pre-injection	30.3 ± 0.5	32.1 ± 0.4	4.8 ± 0.5	4.9 ± 0.7	0.31	0.74
1st m	31.8 ± 0.7*	32.5 ± 0.6*	4.1 ± 0.6*	3.7 ± 0.7*	0.01	0.04
3rd m	32.5 ± 0.6*	32.6 ± 0.3*	3.5 ± 0.3*	3.1 ± 0.2*	0.04	0.03
6th m	30.4 ± 0.3	33.2 ± 0.8*	4.8 ± 0.6	3.5 ± 0.2*	0.03	0.03

SNCV sensory nerve conduction velocity (m/s), **DML** distal motor latency (m/s), **DX** dexamethasone group, **MZ** midazolam group. Data are expressed mean ± standard deviation. (*) significant difference to the base line value. $P < 0.05$ is considered statistical significance.

The electrophysiologic study demonstrated that the sensory nerve conduction velocity (SNCV) was significantly higher in the midazolam group in comparison to the dexamethasone group during the whole study period, and significantly increased within each group in comparison to the basal reading in all patients, except in the 6th month's evaluation of the dexamethasone group. The distal motor latency (DML) was significantly lower in the midazolam group in comparison to the dexamethasone group during the whole study period and significantly decreased within each group in comparison to the basal reading in all patients, except in the 6th month's evaluation of the dexamethasone group where it showed a higher value than its basal reading (Table 5).

No complication, related to the maneuver and during the follow-up period, was detected.

4. Discussion

This study has involved 134 patients with CTS irresponsive to conservative treatment of more than 6 months duration. They were enrolled and randomly allocated into two groups either to received intracarpal dexamethasone or midazolam.

Results of this study revealed that midazolam has offered rapid onset significant reduction of pain in such group of patients. The same result regarding dexamethasone regarding pain relief just up to the 1st month; however, the pain was rebounded and re-increased by the 6th month.

Mechanical decompression of the MN has offered very favorable results as evidenced by many studies. WU et al. denoted that just hydrodissection in the area surrounding MN could be beneficial in comparison to the conventional modes of management of mild to moderate CTS over 6 months follow-p duration [19]. Elawamy et al. also compared hydrodissection of MN with saline versus Hyalase in 60 patients with mild-moderate CTS and found improvement in VAS and functional disability score in both groups, yet they found more favorable results with Hyalase over a duration of 6 months of follow-up [20].

Intracarpal steroid injections have shown very beneficial effects upon CTS symptoms through their anti-inflammatory and anti-edematous effects, especially in patients with mild to moderate CTS [4]. However, local injection of steroids is not devoid of side effects as documented by Brinks et al., in their systematic review. The complications may include local fat atrophy skin pigmentation, fasciitis, cellulitis, skin rash, and skin hypopigmentation [5,6].

Due to such drawbacks of steroids, the authors investigated another novel adjuvant to bupivacaine such as midazolam. The benefits of local midazolam use are the safe hemodynamic profile, low cost, rapid action. Additionally, midazolam is assumed to have one of the best benzodiazepine metabolic profiles [21]. Yilmaz and his colleagues mentioned that the actions of midazolam regarding nerve block and sometimes neurotoxicity are different and separate. Its agonistic action upon the translocator protein enhances the anti-inflammatory action; hence, decreasing the neurotoxicity chance [22].

We assume that this is the first study that denotes the value of intracarpal injection of midazolam. It has been established that GABA receptors are available in the peripheral nerves, especially in the extrasynaptic areas of myelinated nerves [23]. The safety of midazolam was

evaluated by Brian et al., where they compared single-injection formulations of clonidine, buprenorphine, and dexamethasone when mixed with either bupivacaine or midazolam in rats. They found that both combinations produced reversible nerve block without residual effect or nerve damage to sciatic nerves/dorsal root ganglia [24]. In Prasad et al., review, they also have declared the safety of midazolam among other local anesthetics' adjuvant when used for peripheral nerve block in the context of postoperative pain control and chronic pain prevention. The review proposed multimodal actions of midazolam [25].

For acute pain, the addition of midazolam to local anesthetic is well established to hasten the onset of block or offer better postoperative analgesia. Trivedi and Patel compared clonidine 150 mcg versus midazolam 5 mg as additives to 20 ml bupivacaine 0.5% and 10 ml lignocaine 2% for the supraclavicular approach of brachial plexus block in upper limb orthopedic surgeries. The patients were randomized into two groups (30 in each group). They have found that clonidine offered a little bit of analgesia time prolongation (VAS < 3 for 360 minutes in the clonidine group, and 300 minutes in the midazolam group) [26]. El Kenany et al. recruited 82 ladies scheduled for total abdominal hysterectomy randomized into two groups in a 1:1 ratio. The Control group received transversus abdomnis block with 20 mL of 0.25% bupivacaine with 2 ml saline 0.9% (as placebo) while the midazolam group received the same block but with adding 50 mcg midazolam/kg within the 2 ml saline. Postoperative 24 hours morphine consumption, analgesia duration, pain score, sedation score, and adverse events were recorded. They reported longer postoperative analgesia with less consumption of morphine consumption after open hysterectomy with no accountable clinical signs of neurotoxicity (local or systemic) in the midazolam group [27].

For chronic pain, Dureja and coworkers, in patients with lumbosacral postherpetic neuralgia of 3–6 months duration, studied the efficacy of intrathecal midazolam 2 mg in a group, to epidural methylprednisolone 60 mg in another group, and lastly mixing both modalities in a group (50 patients in each group). They found longer pain relief in the mixed group with significantly lower analgesic needs [28].

On the other hand, the use of dexamethasone for acute pain management as an adjuvant to local anesthetics has been implemented and used with variable doses of 1–8 mg in interscalene and supraclavicular nerve block [29]. Although dexamethasone has been utilized frequently and studied for analgesia prolongation when used in the peripheral nerve blocks, the exact mechanism for such effect is still unclear [30].

Our findings regarding BCTQ (SSS and FSS), CSA of the median nerve, sonographic findings (ES, MS, and VS), and MN conduction study (SNCV and DML) showed improvement in both groups up to the third month; however, the beneficial effects were extended to the 6th month in the midazolam group only. This offers a better-sustained effect by midazolam in comparison to dexamethasone.

This study's results are in line with the research done by Cartwright and coworkers who included 19 patients with CTS who have received an intracarpal injection of a mix of 1 ml of lidocaine and 1 ml of triamcinolone acetonide (40 mg). They followed up with the patients regarding ultrasound and nerve conduction changes over 6 months. The nerve CSA was significantly decreased ($p < 0.001$), nerve mobility score increased ($p < 0.001$), and nerve vascularity decreased ($p = 0.042$). Nerve sonographic improvement was noted early by the 1st week [31].

On the other aspect, dexamethasone was included in a study done by Alsaeid et al. and our results agree with their work. They compared MN hydrodissection by hyaluronidase in comparison to dexamethasone. The results in 40 patients with mild to moderate CTS upon BCTQ, CSA of the median nerve, sonographic findings, and nerve conduction study. They found improvements in all parameters in both groups up to the 3rd month, but hyaluronidase has given sustained effect to the 6th month follow-up [16].

Mohammadi et al. mentioned that the best cutoff point of median nerve CSA for the appearance of CTS is 8.5 mm^2 at the tunnel outlet and inlet [32]. Our study revealed that both dexamethasone and midazolam have decreased the CSA; however, in the midazolam, the CSA reached 11.2 mm^2 in comparison to dexamethasone where the CSA just reached to 13.4 mm^2.

In our study, no complication has been reported throughout the whole study period. Median nerve injury had been reported with intracarpal injections. Kim and Park mentioned that the incidence of injury is known to be very low. If the injury occurred, shooting pain and sensory distortion occurs at the same time of injection [33].

5. Conclusion

intracarpal injection of midazolam is superior to dexamethasone in mild to moderate CTS patients as it offers a longer duration of pain relief, higher hand functional improvement scores, and better electrophysiological and sonographic criteria of the median nerve.

6. Recommendations

We suggest comparing midazolam with other established complication-free intracarpal injections, such as Hyalase and/or ozone.

Disclosure statement

The authors declare that there is no conflict of interest

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