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REVIEW

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Efficacy and safety of botulinum toxin-A in writer's cramp: a systematic review, meta-analysis, and meta-regression

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Abstract

Background: Botulinum toxin-A (BoNT) reduce over-firing of dystonic muscles, spasmodic contractions by enhancing function. We conducted a systematic review and random-effects meta-regression to investigate the efficacy and safety of BoNT in writer's cramp (WC). Published electronic articles from inception till January 2022 were screened from four databases (Medline, Science Direct, Scopus, ProQuest). Effect sizes in the form of standardized mean differences were calculated for estimation of efficacy.

Results: Nineteen studies [six randomized control trials (RCTs) and 13 observational studies] involved 587 (514 experimental; 73 Controls) participants with mean age of 43.46 ± 8.84 years with mean duration of WC of 8.31 ± 5.35 years. Injection did not result in significant improvement in writing speed [standard mean difference (95% CI) 0.06 (− 0.35, 0.46)]. There was no significant difference in writing speed as compared to controls [standard mean difference (95% CI) − 0.51 (− 2.55, 1.52)]. The meta-analysis of observational studies showed a significant difference in the mean WC rating score [standard mean difference (95% CI) 0.54 (0.20, 0.88)]. Pooled analysis (observational studies and RCTs) demonstrated a significant difference in the mean Writer's cramp rating score (WCRS) after BoNT [standard mean difference (95% CI) 0.75 (0.06, 1.44)]. No major safety concerns were reported in the included studies.

Conclusions: According to the meta-analysis of observational studies, BoNT injections are effective in WC for improving WCRS without major safety concerns. However, according to the meta-analysis of RCTs, there was no significant effect in efficacy with BoNT.

Keywords: Efficacy, Safety, Botulinum toxin, Writer's cramp

Background

Dystonia is a movement disorder characterized by sustained involuntary muscle contractions resulting in twisting, repetitive movements, or abnormal posturing during activity or at rest. Symptoms of dystonia can range from severe, generalized to focal task-specific problems [1]. Dystonia can affect face, eyelids, oromandibular area, laryngeal, and neck or limbs. Limb dystonia can be observed in the upper and/or lower extremities. Upper extremity dystonia is also termed focal task-specific hand dystonia (FTHD) which comprises the most common form of writer's cramp (WC), musician's dystonia, and occupational dystonia. Writer's cramp is a type of task-specific handwriting disorder described by uncontrollable contractions of agonist and antagonist muscles during an attempt to write of idiopathic origin related to the basal ganglia [2]. Improper force production and failure to maintain the equilibrium between agonists and antagonists' muscles indicates a weakened effort to process sensory information leading to increased cortical excitability. Hence, swift isometric force changes during the voluntary handwriting specific tasks in the wrist and

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forearm muscles, resulting in uneven writing pressure changes in grip force [3].

Botulinum toxin (BoNT) injections have been used in the treatment of reducing symptoms in WC. It acts on the intrafusal and extrafusal muscle fibres thereby preventing the co-contraction of both agonists and antagonist muscles. This physiological effect has been effectively used to control excessive involuntary muscle contractions, and pain. Botulinum toxin acts via selective chemo denervation thereby reducing the effect on muscle spindle afferents given in the selected hand muscles over-activated in the handwriting task. The main disadvantage of BoNT is the short-term effect and the chances of impairment returning to the pre-treatment level are high. Non-pharmacological treatment post-BoNT can effectively work during this period helping in long-lasting improvements with a low risk of side effects [4].

Zakin and his colleagues reviewed six randomized controlled trials (RCTs) for evaluating the efficacy of BoNT therapy and reported 73% response for pooled data of 139 patients in FTHD (WC and musician's dystonia) [5]. A systematic review and meta-analysis by Ashworth and his colleagues, evaluating efficacy of BoNT-A for the treatment of FTHD was not conclusive due to the inclusion of only three trials [6]. The objective of this meta-analysis is to evaluate efficacy and tolerability of BoNT in WC.

Methods

The systematic review protocol was prospectively registered in the International Prospective Register and Dissemination from the University of York (PROSPERO CRD42021272684); https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021272684. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement was utilized [7]. A comprehensive electronic search was performed from four databases—Medline, Science Direct, ProQuest, and Scopus till 31st August 2021. using keywords 'Botulinum toxin' AND 'Writer's cramp' AND 'Efficacy' AND 'Safety'**.** A repeat search was conducted before the final submission and at this stage, one study was added (Likachev and colleagues) [8].

All RCTs, non-randomized observational studies, case–control studies, and case series in which BoNT was used for the treatment of WC were included in the meta-analysis. All types of reviews, case reports, and letters to editors were excluded. Studies involving other focal hand dystonia and/or musicians dystonia, occupational dystonia, and studies conducted on animals and published in other than the English language were also excluded. The titles and abstracts of the articles were screened independently by two reviewers (A.P. and S.Z.). The Rayyan QCRI software blinded these two reviewers and duplicates were removed. Any disagreements between two reviewers were resolved by the third reviewer (A.K.) [9]. Hand search and grey literature search was also conducted to avoid overlooking other eligible articles.

After the identification of 1253 articles for screening of titles and abstracts, three articles were added by manual and grey literature search (Fig. 1). In all, 16 full texts articles were included and retrieved for analysis. Apart from these 16 articles, three additional studies were added as part of the grey literature search. Studies conducted by Jackman and colleagues, and Rajan and colleagues were retrieved from academic libraries and hand search of reference citations [10, 11]. Full-text of article by Behari and colleagues not available initially was later retrieved from an academic library [12]. In addition, three studies were in other than in the English language Koelman and colleagues (Dutch), Marion and colleagues (French), Likachev and colleagues (Russian) [8, 13, 14]. The authors were contacted for providing the manuscript in the English language if they have, and then the three non-English studies were translated into the English language and then included for analysis. To sum it all, a total of 19 studies were included for a full-text analysis in the systematic review.

The data extraction form retrieved data pertaining to study details (author, year of publication, country of trial conduction, study design), population (age group of study population, sample size), outcomes (evaluation parameters or outcomes, presence of control group, comparator if any, type of blinding), and intervention (dosage of BoNT-A, duration of treatment, frequency of injection, efficacy, and safety reporting). The risk of bias assessment was performed using the revised Cochrane risk-of-bias assessment tool (RoB Version-2) and ROBINS-I [15, 16]. We assessed the random sequence generation, concealment of allocation, blinding of participants, personnel and outcome assessment, incomplete data outcome, selective reporting of outcomes, and other biases. The categorization for classification was 'low risk', 'high risk', and 'unclear risk' ROBINS-I domains. Risk of bias Assessment was performed using the Cochrane Risk of Bias 2: a revised tool for assessing the risk of bias for RCTs. ROBINS-I tool was used for assessing the risk of bias for observational study designs (observational; case–control) using Revman software (version 5.4. The Cochrane Collaboration, 2020), by the two (A.P. and S.Z.) reviewers independently, disagreements if any were resolved by the third reviewer (A.K.) [17]. The risk of bias assessment was examined for each observational study (Fig. 2), whereas the risk of bias for RCTs was plotted in the form of traffic light plots along with the forest plots in the meta-analysis. A random-effect model was chosen

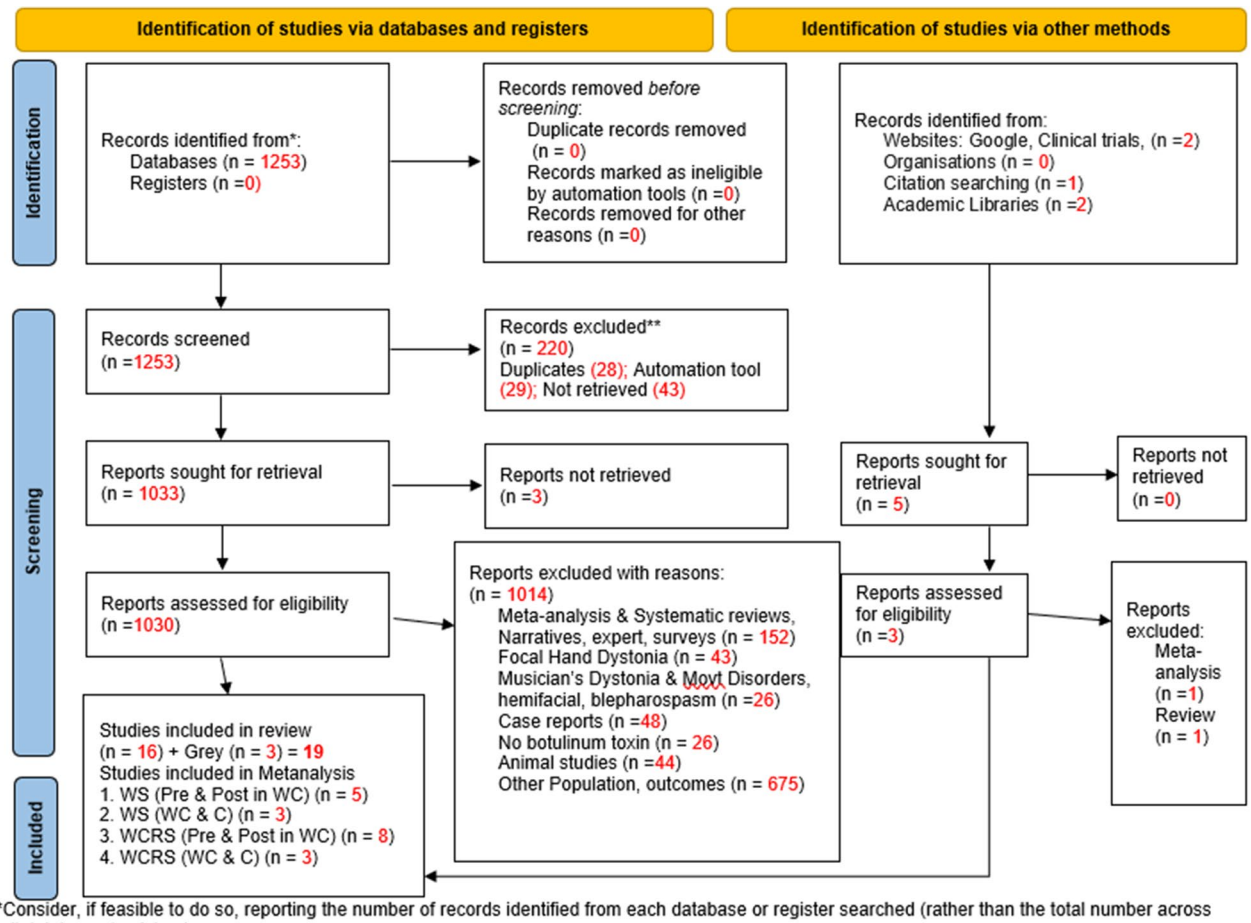

Fig. 1 PRISMA 2020 flowchart for including studies in the systematic review

due to anticipated heterogeneity amongst the included studies using the JASP software (version 0.16.1, 2013, Netherlands) for meta-regression [18]. After observing homogeneity amongst the included studies in the functional outcome measures, meta-analysis was performed for two outcome measures WCRS and WS.

The studies were classified depending on the outcome measures used to calculate heterogeneity via standard mean difference and I^2 statistics in the mean values of Writing Speed (WS) and Writer's Cramp Rating Score (WCRS) scores as described in Table 2 [25]. An I^2 statistics value of more than 60% was assumed as having considerable to high heterogeneity with 95% confidence intervals (C.I.) [19]. A subgroup analysis was then conducted for WCRS based on the study design, observational, and RCT. We also investigated the potential moderators such as age of onset and duration of the condition in WC using meta-regression. We also performed comparative meta-analysis to estimate the differences in each domain in WC and controls by calculating effect sizes by Hedges *g*, Cohens *d*, and 95% C.I. [20]. Quality assessment was conducted using the NIH Quality Assessment Tool for Observational Cohort and cross-sectional studies [21, 22]. Publication bias was assessed and adjusted for with trim and fill adjusted analysis to exclude the outliers if any until the funnel plot of eight studies was plotted till it became symmetrical with the adjusted effect size [23]. In addition to the visual methods of interpretation, Egger's test was applied for statistical inference for detection of publication bias. Adjustment using the Duval and Tweedie trim and fill method was done to impute the studies on the left side of the funnel plot and recompute the combined effect under the random-effects.

Four traffic light plots were plotted after the respective studies qualified the criteria according to similarity observed in terms of methodology and outcomes utilised to measure function and impairment. The four analyses

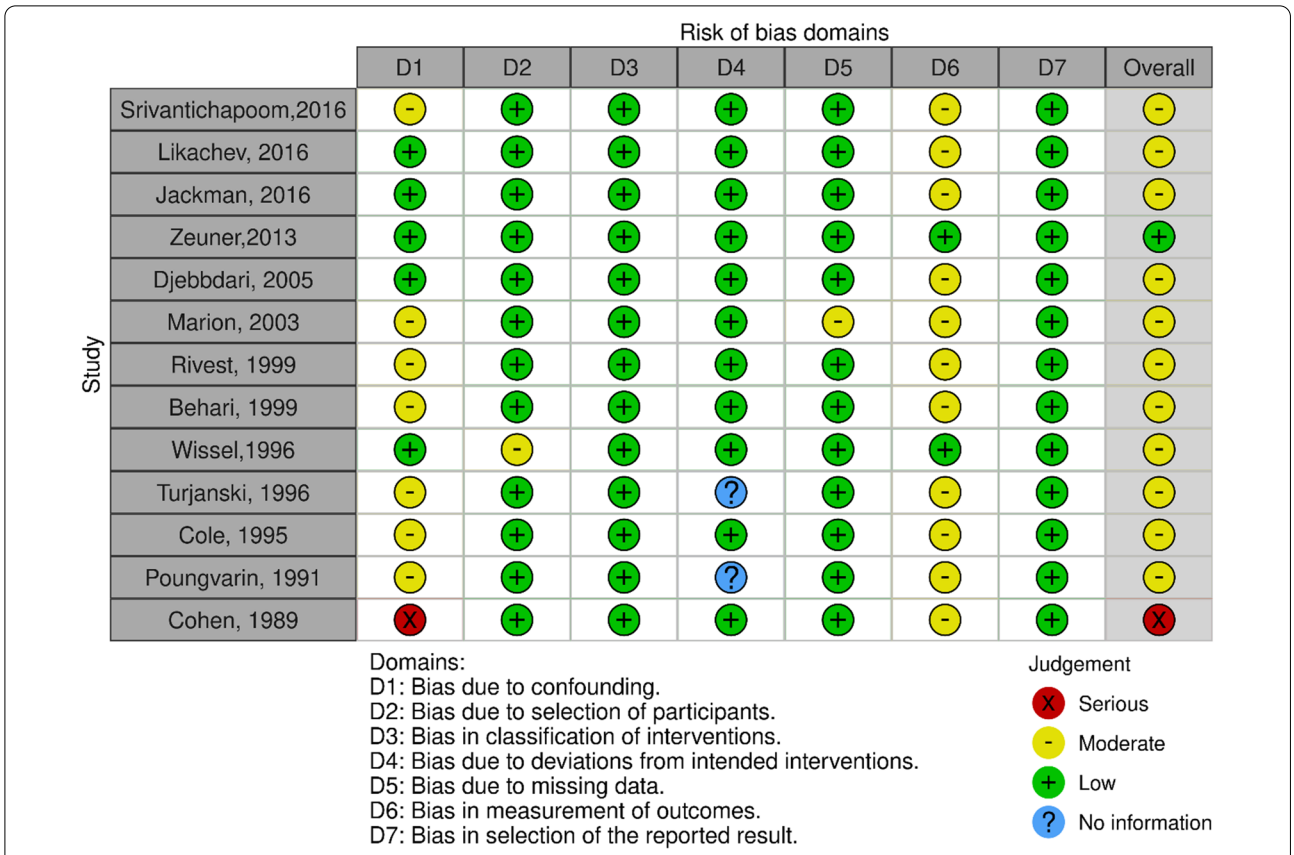

Fig. 2 Risk of bias assessment for observational studies using ROBINS-I tool

were: (a) WS outcome pre and post BoNT in WC (Wissel and colleagues, Chen and colleagues, Behari and colleagues, Kruisdijk and colleagues, Contarino and colleagues, Rajan and colleagues) [11, 12, 24–27] (b) WS outcome in WC and Controls (Kruisdijk and colleagues, Contarino and colleagues, Rajan and colleagues) [11, 24, 26] (c) WCRS outcome pre and post BoNT in WC with subgroup analysis (Four observational: Wissel and colleagues, Zeuner and colleagues, Jackman and colleagues, Likachev and colleagues, and Four RCTs:: Chen and colleagues, Kruisdijk and colleagues, Park and colleagues, Rajan and colleagues [8, 10, 11, 24, 25, 27, 29, 30] (d) WCRS outcome in WC and Controls (Kruisdijk and colleagues, Jackman and colleagues, Rajan and colleagues) [10, 11, 24]. Sensitivity was investigated by not considering the study with a broad C.I. (Chen and colleagues) (Fig. 4) [25].

Results

Summary of study characteristics are provided in Table 1. Other study details include the dose, frequency, and duration of BoNT therapy, efficacy parameters WCRS and WS, and safety are shown in Tables 2 and 3. A total of six RCTs and 13 observational studies included 587 (514 WC and 73 Controls) participants with a mean age of 43.46 ± 8.84 years. The mean duration of the condition was 8.31 ± 5.35 years. Six studies had a control group, whereas only one study assessed the effect of occupational therapy along with BoNT (Park and colleagues) (Table 1) [30].

Nine out of 19 studies were blinded (one was quadruple-blinded, four were double-blinded, four single-blinded). WS was assessed in four studies (Wissel and colleagues, Behari and colleagues, Chen and colleagues, Kruisdijk and colleagues, Contarino and colleagues, Rajan and colleagues) [11, 12, 24–27], whereas WCRS score was assessed in 8 studies (Wissel and colleagues, Chen and colleagues, Kruisdijk and colleagues, Zeuner and colleagues, Likachev and colleagues, Jackman and colleagues, Park and colleagues, Rajan and colleagues) [8, 10, 11, 24, 25, 27, 29, 30] (Table 2).

Botulinum toxin A injection usage was reported in all studies of which a total of nine studies reported the manufacturer's name. The types of BoNT-A used were Incobotulinum toxin A (Xeomin), Ona botulinum toxin A and Oculinum toxin A. The mean dosage differed based

Table 1 Characteristics of included studies

Study	Study design	Study population	Age of study population	Duration of WC	Sample size
Rajan, 2021	RCT	DT, C	46.0 ± 18.6	8.5 ± 5.8	15 (DT), 15 (C)
Park, 2019	RCT	WC	62.0 ± 6.0	21.0 ± 3.0	6 (WC), 6 (C)
Srivantichapoom, 2016	Observational	WC, C	47.9 ± 6.3	19.1 ± 5.9	8 (WC)
Jackman, 2016	Observational	WC (responders), C (non-responders)	59.8	12.3 ± 11.2	5 (WC: responders), 4 (WC: non responders)
Likachev, 2016	Observational	WC	39.7 ± 4.5	5.8 ± 0.65	29 (WC)
Zeuner, 2013	Observational	WC, C	57.1 ± 10.7	10.9 ± 8.8	10 (WC), 18 (C)
Contarino, 2007	RCT	WC	36.9 ± 9.7	9.3 ± 8.9	29 (WC) 10 (C)
Kruisdijk, 2007	RCT	WC	47.60 ± 11.24	7.38 ± 6.22	20 (WC), 20 (C)
Djebbdari, 2005	Observational	WC	46.1 ± 14.0	7.6 ± 8.1	47 (WC),
Marion, 2003	Observational	WC	35.6 ± 43.13	4.6 ± 13.43	167 (WC)
Behari, 1999	Observational	WC	35.75 ± 23.33	3.64 ± 8.48	16 (WC)
Chen, 1999	RCT	WC	31.6	–	8 (WC)
Wissel, 1996	Observational	WC	34.8	12.3	31
Turjanski, 1996	Observational	WC, 1 MC	36	–	45 (WC)
Cole, 1995	Observational	WC	49.4	8.5 ± 5.16	10 (6 WC, 2TC, 2MC)
Tsui, 1993	RCT	WC, C	41.75	5.15	20
Rivest, 1991	Observational	WC	43	9	12 (WC)
Poungvarin, 1991	Observational	WC	36.8 ± 10.22	5.88 ± 7.14	25(WC)
Cohen, 1989	Observational	WC	38	7	19 (WC)

WC writer's cramp, *C* control group, *RCT* randomised controlled trial, *MC* musicians dystonia

on the muscles chosen and the severity of the condition. The common muscles for injection in ascending order of affection were deep finger flexors, flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), flexor pollicis longus (FPL) followed by wrist flexors flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), flexor pollicis brevis (FPB), wrist extensors extensor indices (EI), extensor carpi ulnaris (ECU), extensor carpi radialis (ECR), extensor pollicis brevis (EPB), forearm pronators were pronator quadratus and teres (PQ, PT) and grip muscles (lumbricals). The muscles were re-injected at a mean of 9.83 ± 8.80 weeks (range 2–32 weeks) with an average of 2.61 ± 1.20 visits per week during follow-up.

Botulinum toxin was found to be effective in the WC group in all studies (Table 3). Overall, BoNT-A demonstrated a 60–70% improvement. All studies except two studies (Contarino and colleagues, Park, and colleagues) reported the adverse reactions [26, 30]. Weakness in the injected muscles was reported in 12 studies followed by pain at the injection site in five studies and sub-clinical atrophy in one study. Three studies (Djebbdari and colleagues, Contarino and colleagues, Park and colleagues) did not mention safety concerns [26, 30, 35]. Eight studies reported dropouts of 29 patients opting for alternative treatment such as physiotherapy and occupational therapy, five patients discontinued BoNT treatment due to lack of improvement after three successive injections (Wissel and colleagues) [27]. Eighty-seven patients were lost to follow-up or abandoned treatment due to improvement, whereas two dropouts were reported due to poor recording quality of outcomes (Contarino and colleagues), and six patients discontinued due to side effects after the first session [26]

Four traffic light plots revealed injection of BoNT did not result in significant improvement of WS in patients with WC [Std MD (95% CI) 0.06 (− 0.35, 0.46)] (Fig. 3). There was no significant difference in WS after injection of BoNT as compared to the control group in patients with WC [Std MD (95% CI) − 0.51 (− 2.55, 1.52)] (Fig. 3). According to the results of the meta-analysis of observational studies, there was a significant difference in the mean WCRS score with BoNT [Std MD (95% CI) 0.54 (0.20, 0.88)]. Similarly, overall pooled analysis (observational studies and RCTs) also showed a significant difference in the mean WCRS score after injection of BoNT [Std MD (95% CI) 0.75 (0.06, 1.44)]. However, the meta-analysis of RCTs did not show a significant difference in the WCRS after injection of BoNT [Std MD (95% CI) 1.02 (− 0.81, 2.84)] despite sensitivity analysis for Chen and colleagues (Fig. 4) [25]. The meta-analysis of studies did not show a significant difference in WCRS after injection of BoNT as compared to the control group [Std MD (95% CI) 13.22 (− 9.62, 36.06)] (Fig. 4). A

Table 2 Characteristics of outcome measures of included studies

Study	Evaluation parameters	Writing speed		WCRS score	
		Experimental	Control	Experimental	Control
Rajan, 2021	WCRS, WS, PGIC, Total power on spectrum analysis, Grip strength via dynamometer, Fahn-Tolosa-Marin Tremor Rating Scale (A, B, C)	5.0 ± 33.33 (Pre) 5.0 ± 33.26 (Post)	4.3 ± 29.0 (Pre) 4.3 ± 3.33 (Post)	11.6 ± 1.8 (Pre) 7.2 ± 1.2 (Post)	11.2 ± 1.7 (Pre) 8.9 ± 1.3 (Post)
Park, 2019	Patient related subjective scoring score, WCRS, WCIS, WCDS, Handgrip strength, kinetic parameters	NA	NA	8.3 ± 2.8 (Pre) 11.5 ± 3 (Post)	NA
Srivantichapoo m, 2016	Active ROM: forearm, wrist, fingers, DDS Handwriting Scale	NA	NA	NA	NA
Likachev, 2016	WCRS, Symptom Severity Scale, FSS	NA	NA	10 ± 3.53 (Pre) 8 ± 2.82 (Post)	NA
Jackman, 2016	UDRS, Dystonia Movement, Disability Scale DMDS, WCRS, Kinematic analysis	NA	NA	8.5 ± 0.706	5 ± 0.706
Zeuner, 2013	Force sensor, DDS, WCRS	NA	NA	10.37 ± 5.68 (Pre) 8.90 ± 7.13 (Post)	NA
Contarino, 2007	Sensory Evoked Potentials SEP, Writing speed	2.1 ± 1.9/mean change	0.3 ± 1.4 mean change	NA	NA
Marion, 2003	Subjective Handwriting assessment	NA	NA	NA	NA
Kruisdijk, 2007	VAS, FSS, WCRS, Writing speed	7.59 ± 2.80 (Pre) 9.00 ± 2.28 (Post)	7.93 ± 3.20 (Pre) 8.20 ± 2.90 (Post)	4.50 ± 1.96 (Pre) 2.20 ± 1.88 (Post)	4.47 ± 1.184 (Pre) 3.68 ± 1.16 (Post)
Djebbdari, 2005	Burke-Fahn-Marsden Scale, Self-assessment on handwriting quality, DDS	NA	NA	NA	NA
Behari, 1999	Ease of writing, abnormal posture, pain, WS	15.75 + − 5.28 (Pre) 18.92 + 4.9 (Post)	NA	NA	NA
Chen, 1999	Self-reported (benefit scale, VAS, weakness), WCRS, writing speed, writing quality scale	1.47 ± 1.8 (Pre) 1.38 ± 1.3 (Post)	NA	4.9 ± 1.1 (Pre 7.8 ± 0.7 (Post)	NA
Wissel, 1996	WCRS, writing speed, MRC Scale, video recording of writing	1.1 ± 0.5 (Pre) 0.8 ± 0.6 (Post)	NA	9.1 ± 4.5 (Pre) 6.6 ± 4.1 (Post)	NA
Turjanski, 1996	Subjective handwriting assessment, fluency, duration of writing	NA	NA	NA	NA
Cole, 1995	MRC, timed writing, writing errors	NA	NA	NA	NA
Tsui, 1993	Writing speed, Gibson's maze, accuracy pen control	Subjective	NA	NA	NA
Rivest, 1991	Subjective handwriting assessment, fluency, duration of writing	NA	NA	NA	NA
Poungvarin, 1991	Subjective pain, hand tremor assessment in writing	NA	NA	NA	NA
Cohen, 1989	MRC, EMG	NA	NA	NA	NA

VAS visual analogue scale, *SEP* sensory evoked potentials, *ROM* range of motion, *DDS* dystonia disability scale, *WCRS* writer's cramp rating scale, *WS* writing speed, *WCIS* writer's cramp impairment scale, *WCDS* writer's cramp disability scale, *MRC* Medical Research Council, *FSS* functional status scale, *NA* not applicable

total of 111 WC participants, the WCRS scores had a pooled standard mean difference of 0.75 (95% C.I., 0.06 to 1.44; $p = 0.03$) pre and post BoNT injection (Fig. 4). Subgroup analysis revealed highly significant ($p < 0.0001$) values of WCRS scores from RCTs than observational studies. The difference between both study designs was $Chi^2 = 0.25$, $P = 0.61$.

The p-value in both the extremities and overall was $P = 0.74$ (observational) and $P < 0.0001$ (RCT) thereby rejecting the null hypothesis signifying the absence of homogeneity. I^2 statistics indicated a low probability of pooled heterogeneity (Observational = 0%, RCT = 91%, Overall = 81%). The size of the diamond in both the subgroup analyses signified that the intervention favours

Table 3 Botulinum toxin injection data

Study	Blinding	Type of Botulinum Toxin, Dosage	Muscle	Frequency	Visits
Rajan, 2021	Quadruple-blinded	Ona botulinum toxin A (Botox, Allergan) with dilution of 50 U per 1 mL in saline, 0.9%	Wrist flexors (FCR, FCU) were given higher doses than extensors (ECR, ECU)	0, 6, 12 weeks	3 visits
Park, 2019	Double-blinded	Incobotulinum toxin A (Xeomin). Mean total dose 40 MU for 12 patients. (different dosage for different subjects in age and muscle affection (Table 2).	FDS, FPB, ECU, FDP, Lumbricals	20 weeks	2 visits
Srivantichapoom, 2016	None	Not mentioned active ingredient Average Mean Dose 53.4 ± 25.6 MU	FDS, FPB, FPL, FCR, EPL	1st,12 months prior	
Jackman, 2016	None	BoNT-A (Botox; Allergan Inc.: Irvine, CA); (50 units per vial) with 1:1 saline	Muscles were decided according to severity of affection	0,6,16,22,32 week	5 visits
Likachev, 2016	None	Dysport, 236 MU	Muscles of the forearm during rest and during the act of writing	0, 3 weeks, 3rd month, 6th month	1 visit
Zeuner, 2013	Single blinded	Dysport, Ipsen dilution 500 MU per 2.5 ml 0.9% saline	Wrist muscles and/or superficial deep finger flexors. (Specific muscles are not mentioned)	0,2,4,6,8 weeks	5 visits
Contarino, 2007	Double-blinded	Dysport, Ipsen 20 MU/0.1 ml of saline	FPL, FDP, EI	4 weeks	2 visits
Kruisdijk, 2007	Single blinded	Freeze-dried BoNT-A (Dysport, Ipsen Biopharma, Wrexham, UK) diluted to 20 MU per 0.1 ml of 0.9% saline. Mean total dose:224 MU	FPL, FDP, EI	4, 8, 12 weeks	2 visits
Djebbdari, 2005	None	Dysport, 500 U/2.5 ml	FCU, FCR, FDS, FPL, PT, PQ, ECR	1st, last visits varied	varied
Marion, 2005	None	Dysport 80 MU/0.6 ml of saline	FDS, FDP, ECR, ECU	1 month	varied
Behari, 1999	None	Dysport (Speywood), Botox (Allergan, USA)	FDP, FDS, FCU, ED, EI, APL	0, 3, 12 weeks	19 visits
Wissel, 1996	Single blinded	Average mean dose was 133.2 MU. Dysport 60 units (Finger movers), 80units (wrist movers)	FCU, FCR, FDS, FPL, ECR	2 weeks–8 months	2 visits
Turjanski, 1996	None	Botulinum toxin (Dysport, Speywood Pharmaceuticals, UK); Mean dose: 146 + 80 MU	FDP, Extensors of wrist, fingers	Mean follow-up 21 months	
Cole, 1995	Double-blinded	Botulinum toxin-A, 24 MU	FCR, FDS, FPL, FCU, ED	0, 2 weeks, 3 months	3 visits
Tsui,1993	Double-blinded	The dose was 30–50 MU. Not mentioned active ingredient	FDS, FDP, FCU, ECU, PT, PQ	3 months	2 visits
Chen, 1999	Single-blinded	BoNT-A (BOTOX, Allergan, Irvine, CA, U.S.A.; diluted 10 units per 0.1 mL)	FDS, FPL, FPB, FCU, FCR, ECU	0, 2, 6 weeks, 3 months	2 visits
Rivest, 1991	None	Mean dose, 40–60 MU Not mentioned active ingredient	FDP, FCU, FPL, ED, EPL, EI, ECU	0,2 weeks	2 visits
Poungvarin, 1991	None	Botulinum toxin-A, Allergan, California; 20–30 MU	FDP, FCU, FPL, ED, EPL, ECU	2 weeks, 1–2 months	3 visits
Cohen, 1989	None	Oculinum (BoNT-A), 17.5 to 140 MU	FDS, FDP, FPL, ED, EPL	1,3,5 week (27 months follow-up)	3 visits

BoNT Botulinum toxin-A, *MU* mouse units, *ml* millilitres, *FDS* flexor digitorum superficialis, *FDP* flexor digitorum profundus, *FPL* flexor pollicis longus, *FCU* flexor carpi ulnaris, *FCR* flexor carpi radialis, *FPB* flexor pollicis brevis, *EI* extensor indices, *ECU* extensor carpi ulnaris, *ECR* extensor carpi radialis, *EPB* extensor pollicis brevis, *PQ, PT* pronator quadratus and teres

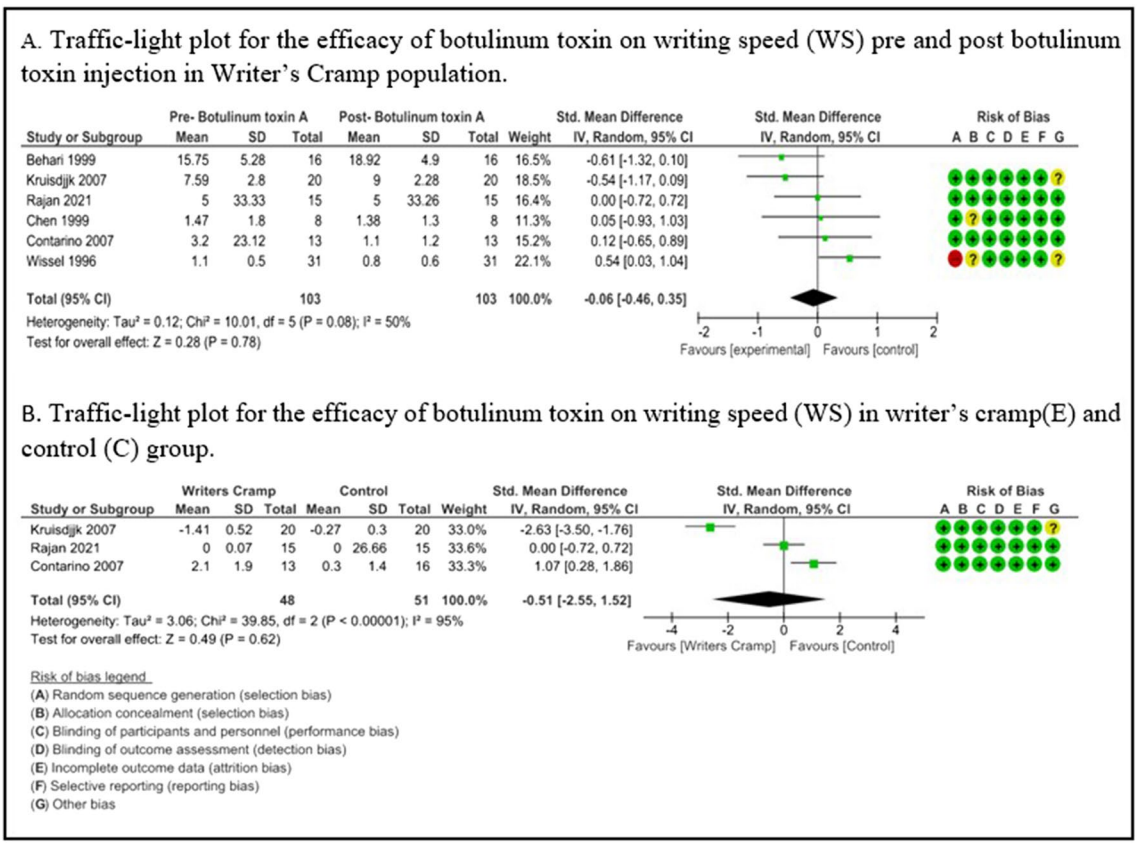

Fig. 3 Traffic light plot for the efficacy of pre and post botulinum toxin on WS in WC (**A**) and in (**B**) WC in Controls

the post BoNT intervention group under the given conditions. Using the eyeball test for visual inspection, the weights of the individual studies appear unequal in size, and the C.I.'s of the continuous data do not overlap in the RCTs, whereas there is overlap in the observational studies, and the summary of the pooled effect estimates is wider for both the study designs. The magnitude of the individual studies is almost equal and overall, the magnitude of the diamond is favouring the post BoNT intervention and there is an overlap of C.I. among the two studies [8, 24]. The direction of the magnitude of the remaining studies favours the post-intervention group, whereas Park and colleagues is the only study which is crossing the midline favouring the pre BoNT condition [30].

The overall quality assessment of individual studies for observational studies is shown in Additional file 1: Table S1. Observational study analysis using the ROBINS-I tool (Fig. 4) showed 'low risk' bias in one study and eleven studies had 'moderate risk'. The most common source of bias in individual studies were due to confounding (D1) in two studies followed by bias due to selection of participants (D2) and bias in the measurement of outcomes (D6). For RCT's the risk of bias was reported as 'low risk' in all domains of individual and overall study biases (randomisation, allocation, blinding of participants and outcomes, incomplete data, and selective reporting) in the form of traffic-light plots (Fig. 3).

Visual inspection of the funnel plot was asymmetric (Fig. 5); Egger's regression test intercept (ßo = − 49.62; $t = 2.821$, p-value = 0.03, 2-tailed) was significant suggesting the presence of publication bias in this literature. The pooled mean of WCRS scores to assess the efficacy pre and post BoNT in WC point estimate is 0.91873 (− 0.51039, 2.34784) and after using Trim and Fill the imputed point estimate is 0.52728 (− 1.16925, 2.22380). The Begg and Mazumdar Rank Correlation test with continuity correction was significant (Kendall's Tau = 0.017; $P = 0.03$, 2-tailed), suggesting that bias does exist and may be due to low statistical power cannot be taken as evidence that bias is absent.

To assess the effect of the predictor variable (moderator) on the treatment effect we chose 'Age of onset' and 'duration of WC' as moderators for meta-regression and adjustment was done using the Duval and Tweedie's trim and fill method. According to the meta-regression analysis, onset

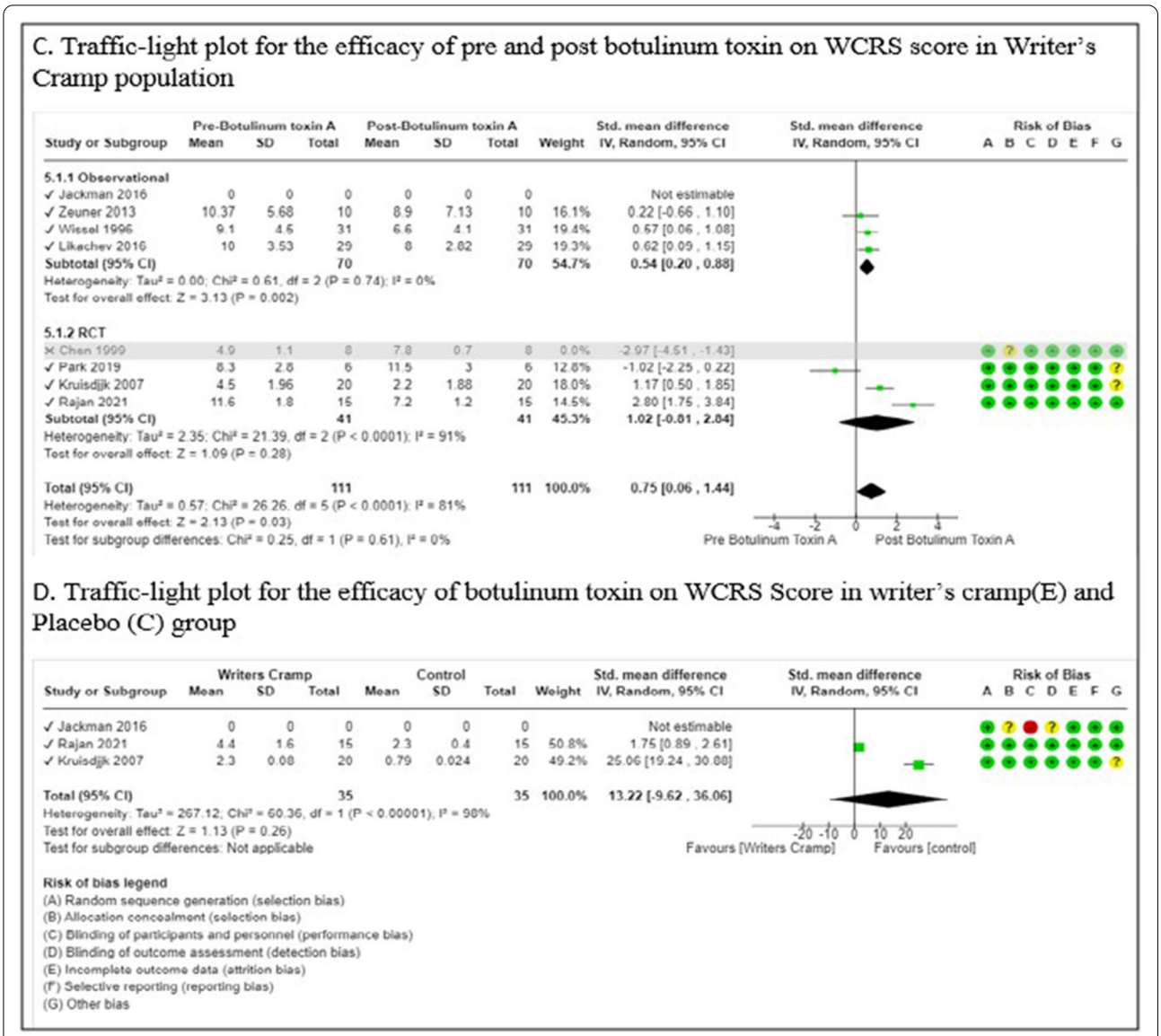

Fig. 4 Traffic light plot for the efficacy of pre and post botulinum toxin on WCRS in WC (**C**) and in (**D**) WC and Controls

of age ($ß = 0.0269$, $p = 0.80$, $Z = 0.25$, $R^2 = 0.04$), and duration of WC condition ($ß = -0.1039$, $p = 0.6101$, $Z = -0.51$, $R^2 = 0.04$) were not statistically significant and, therefore, were not proportional with WCRS scores used to assess efficacy of BoNT in WC (Additional file 1: Table S2).

Discussion

Dysport injection as a form of BoNT-A was most used in almost all the studies except for Park and colleagues, who used Xeomin as a form of BoNT-A [30]. Out of the available types of BoNT from A TO H, type-A was used in all studies (Table 3) [2]. Tsui and colleagues, Kruisdijk and colleagues, Contarino and colleagues used 20 Mouse Units of the Dysport injection which was diluted to 0.1 ml of 0.9% saline [24, 26, 33]. Park and colleagues, Srivantichapoom and colleagues, Wissel and colleagues, and Zeuner and colleagues reported using different subjective concentrations of the injection depending on the muscles it was injected, expertise, and previous reaction to BoNT, if any [27, 28, 30, 34].

Not all studies were analysed in a similar fashion for handwriting assessment. Tsui and colleagues assessed WS and accuracy pen control with a Gibson's maze analysis but was subjective in nature on 20 WC participants [31, 32]. WCRS and WS scores were applied in six out of 19 studies only except for Tsui and colleagues

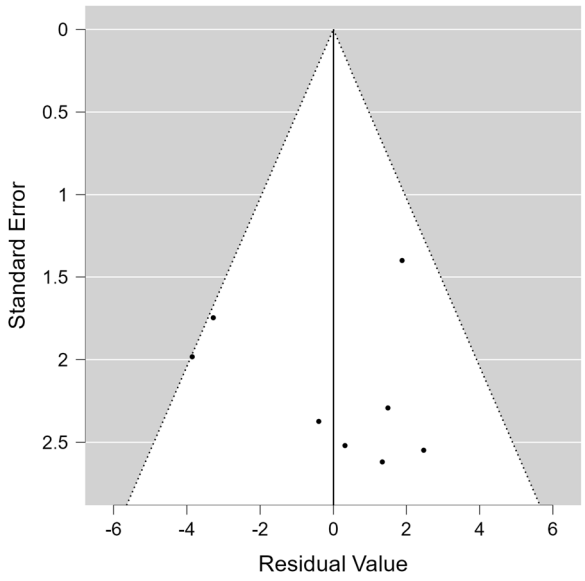

Fig. 5 Funnel plot for detection of publication bias

and Srivantichapoom and colleagues who used Dystonia Disability Scale and ROM as measuring parameters [33, 34]. The other parameters extracted from the included studies were Writing speed and WCRS score as they were the only commonly found outcome measures in the 19 included studies. The mean values are provided in Table 2. Intramuscular injections of BoNT-A were used in all studies. Six out of 19 studies (Contarino and colleagues and Kruisdijk and colleagues) conducted their trials in controls, whereas three studies. Wissel and colleagues, Zeuner and colleagues and Park and colleagues evaluated the pre- and post-effect and their WCRS scores were reported accordingly [24, 26, 27, 29, 30]. All injections were guided using electromyography along with outcome measures such as pain, the severity of symptoms, range of motion (ROM) in fingers, wrist, and forearm, Dystonia disability scale along with WCIS, WCDS were used. The average duration of treatment was 8–12 weeks ranging from 2 to 32 weeks. The average frequency was at least 2 sessions in total in all studies except one study (Zeuner and colleagues) reported a single session of BoNT-A injection [29].

WCRS is an outcome measure that comprises of two domains, the writing movement score and the writing speed sub score which distinguishes dystonic posture, the latency of dystonia, and writing tremor by grading it as 0, 1, 2 (no, moderate, marked, respectively) pathological movement [28, 35]. BoNT-A has demonstrated efficacy in the treatment of WC for WCRS outcome measures with few adverse effects were reported such as muscle weakness, pain at the injection site. All reported adverse effects reported were not serious adverse effects [36, 37]. Significant results although observed in WCRS than WS can be reflective of the fact that is WS a good indicator for estimating function in WC?. More than the speed of handwriting it is the quality of the letters produced, the technique of writing, and the posture of the forearm while attempting the task are matters of major concern in the productive age group of 30–40 years.WS did not show significant results on efficacy, probably because the quality of handwriting and endurance of the muscles resulting in the legibility of letters involved in the task of handwriting are more relevant parameters than the speed of completing the letters in a stipulated amount of time [38, 39].

Muscle weakness was reported in the form of finger drop, inability to use the 2nd and 3rd fingers, transient lasting for a period of 1 week to 2 months, anywhere between mild to a severe reduction in muscle strength. Muscle atrophy though reported was sub-clinical due to secondary cumulative injections, pain at the site of the injection, other descriptors were short-lasting lethargy, discomfort while writing, feeling of awkwardness, mild flu-like symptoms, arm fatigue, and skin hematoma. Kruisdijk and colleagues reported weakness in hand (18 WC, two C), pain at the injection site (one WC, three C) with a total sample of 20 [24]. Wissel and colleagues reported 72% of the total sample size of 31 reported weakness as the most common side-effect, whereas Zeuner and colleagues reported all 10 patients reported weakness in the injected muscles [27, 29]. Reasons for loss to follow-up or abandonment could be the short-duration effect of BoNT-A, cost of the injection, and the side effects even though minimal or relative [40, 41]. Weakness although transient in nature but is inevitable as observed across studies. In addition, the use of electromyography for injection guidance can be frustrating even before the actual procedure instead real-time ultrasonography guidance can be a better option being non-invasive, radiation-free as used by Behari and colleagues, Likachev and colleagues [8, 12]. Side effects can be reduced and follow-up can be increased by increasing the interval between subsequent visits of BoNT-A. Non-pharmacological treatment options such as rehabilitation alongside BoNT-A can be considered a better option to relax the abnormal firing by the spasmodic agonists and also aid in the recruitment of the weaker muscles [13].

A combination of study designs often results in a high level of heterogeneity as observational studies are more biased and lack randomization. Although, in view of the same population, use a control group to observe the effect of the same outcome measures (WCRS and WS). We chose to combine yet separate by choosing a sub-group analysis and presenting a pooled estimate of

observational studies in one group and RCTs in another. The results were then compared and discussed using the pooled estimates. Hence, the applicability of the results of the meta-analysis was proven statistically significant and reported no major adverse effects thereby making it clinical applicable too. The choice of combining the meta-analysis for two different study designs was made in this situation as the population in which the studies were conducted has a rare incidence. Out of all the studies conducted in WC, overlapping of WC with other types of dystonia has a higher possibility and thereby the approach to treatment differs on a case-to-case basis. Although, the outcomes of WCRS and WS came out to be strikingly similar in all the published literature with BoNT as the intervention. All in all, combining two entirely different designs with an almost similar methodology resulted in more biases for non-randomised (observational) studies but for estimating the dose response for efficacy and safety using functional outcomes, sub-group analysis proved beneficial.

Reasons for heterogeneity was probably due to many contributing factors including the methodology, intervention, different dosages depending on the severity and duration of dystonia affecting functional limitation, frequency of visits, compliance of the patient and treatment in anticipation of any adverse effects and follow-up contributed to clinical and statistically significant heterogeneity, and therefore, a random-effect model was chosen. Amongst the four traffic-light plots (forest plot along with a risk of bias analysis), only one forest plot (c) was plotted for detection of funnel plot, as the minimum criteria required to plot is 6–8 studies. (Fig. 5). Jackman and colleagues had presented the WCRS scores values as mean difference change, as the mean and standard deviation values were not available for meta-analysis of two different groups [10]. The authors were contacted for providing values of pre and post BoNT A injection using WCRS scores. Addition of these values in the meta-analysis would have been a great asset in the interpretation of results of the WCRS outcome. Hence, in the forest plots the values were written as 'not estimable' (Fig. 4) [10].

Deep finger flexors were more affected followed by wrist flexors, ulnar deviators, pronators, and wrist extensors also. Dominance also plays a crucial role in determining the severity of the cramp associated with the abnormal firing of agonists and antagonists. Handwriting is not the only task hindered in activities of daily living (ADLs), difficulty and/or anxiety may also extend to other ADLs such as typing, using a spoon, buttoning, and other fine motor activities [12]. Those who develop the cramp in one extremity begin to write with the other extremity and compensate for the handwriting part when required in daily life. However, over a period, the cramp is observed in the other extremity as well signifying that the pathology is not just involving the muscle but has a central mechanism involvement at various levels of motor control inclusive of the spinal cord, basal ganglia, and motor cortex. Loss of supra-spinal inhibitory control leads to loss of selectivity leading to an overflow in recruitment. BoNT works at the gamma motor neuron at the muscle spindle and alpha motor neuron at the neuromuscular junction [42]. Nevertheless, BoNT came into existence in the treatment of dystonia as the 'miracle poison' [4]. Non-pharmacological alternatives such as rehabilitation in the form of physical therapy and occupational therapy can work at two levels addressing the recruitment of the antagonists and the secondary biomechanical concerns [5]. Post-injection weakness and disability may not entirely be due to the toxin itself, but it may have already existed due to prolonged dystonia in the affected muscles. Rehabilitation becomes, therefore, imperative alongside a pharmacological treatment option to reduce the involuntary inhibition [43]. However, the rate of referral to a rehabilitation specialist can be quite low if the pathological mechanism is not clearly understood by the referring physicians, patients, and the rehabilitation specialists.

Inclusion of published literature of all study types, combined a mixed study design, use of respective tools for identifying biases, inclusion of grey literature from electronic sources, academic libraries and most importantly translation of the non-English literature from three different languages (French, Dutch and Russian) are major strengths of our meta-analysis.

Relatively small sample size is a limitation of this meta-analysis. Only six RCTs were reported in WC which had objective outcomes. We found no relationship with the 'age of onset' and 'duration of symptoms' of WC; this relationship may be explored further with other independent variables. Lack of long-term follow-up is other limitations of the available studies with BoNT-A. All the reported adverse effects are short-term in nature. It would be interesting to devise strategies to understand reasons for the loss to follow-up and work on increasing the duration of the interval between two consecutive injections. An amalgamation of pharmacological and rehabilitation treatment can be an interesting arena for future studies. There is a need to conduct more RCTs with consistent and objective outcome measures accompanied by a clinically consistent dosage of the BoNT injection to produce minimal side effects. It should also be noted that all studies used variants of BoNT-A and are different products, hence a meta-analysis with a single product type is needed and can be a possibility for prospects.

Conclusions

Meta-analysis of observational studies suggests that BoNT injections are effective for the WCRS outcome measure, without major safety concerns when used in patients with WC. However, according to the meta-analysis of RCTs, there was no significant effect in efficacy with BoNT. Based on the 'age of onset' and 'duration of symptoms' in WC, there was no significant effect on the improvement of WCRS scores.

Abbreviations

BoNT: Botulinum toxin; C: Control group; DDS: Dystonia disability Scale; FTHD: Focal task-specific hand dystonia; FDS: Flexor digitorum superficialis; FDP: Flexor digitorum profundus; FPL: Flexor pollicis longus; FCU: Flexor carpi ulnaris; FCR: Flexor carpi radialis; FPB: Flexor pollicis brevis; EI: Extensor indices; ECU: Extensor carpi ulnaris; ECR: Extensor carpi radialis; EPB: Extensor pollicis brevis; FSS: Functional Status Scale; H: High; L: Low; MC: Musicians dystonia; MU: Mouse units; Ml: Millilitres; MRC: Medical Research Council; NA: Not applicable; NR: Not reported; PQ: Pronator quadratus; PT: Pronator teres; ROM: Range of motion; RCT: Randomized controlled trials; SEP: Sensory evoked potentials; UC: Unclear; VAS: Visual Analogue Scale; WCRS: Writer's Cramp Rating Scale; WCIS: Writer's Cramp Impairment Scale; WCDS: Writer's Cramp Disability Scale; WC: Writer's cramp; WCRS: Writer's Cramp Rating Scale; WS: Writing speed.

Supplementary Information

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Additional file 1: Table S1. Studies assessed using the NIH Quality Assessment Tool for Observational cohort and Cross-sectional studies. **Table S2.** Meta-Analysis and Meta-Regression for WCRS scores in WC

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Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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