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Assessment of the risk of musculoskeletal adverse events associated with fluoroquinolone use in children

A meta-analysis

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Abstract

Background: The use of fluoroquinolone antibiotics has been restricted in children because of their potential to cause adverse musculoskeletal events. This study was performed to systematically evaluate whether there is a difference between fluoroquinolone and non-fluoroquinolone antibiotics in terms of their associated risk of adverse musculoskeletal events in children.

Methods: Cochrane Library, Embase, and PubMed databases were used to retrieve studies related to fluoroquinolone and non-fluoroquinolone-induced musculoskeletal adverse events in children. A meta-analysis was performed using Stata 11.

Results: A total of 10 studies were included in the analysis. The combined results showed that there was no statistical difference between fluoroquinolone and non-fluoroquinolone groups in terms of musculoskeletal adverse events in children (risk ratio = 1.145, 95% confidence interval = 0.974–1.345, $P = .101$). Subgroup analysis was performed using a random-effects model. Here, the effects on the trovafloxacin and levofloxacin groups were significantly different from that of the control group. However, musculoskeletal adverse events due to either drug was not reported after long-term follow-up.

Conclusions: The results showed that fluoroquinolone and non-fluoroquinolone antibiotics were not different in terms of their ability to cause musculoskeletal adverse events in children. For this reason, fluoroquinolone antibiotics can be used in children as appropriate.

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Abbreviations: CI = confidence interval, FDA = food and drug administration, RCT = randomized controlled trial, RR = risk ratio.

Keywords: fluoroquinolone, musculoskeletal adverse events, side effects

1. Introduction

Fluoroquinolones are unique antimicrobial drugs. By targeting bacterial topoisomerase in the nucleus, including DNA helicase and topoisomerase IV, they block progression of the DNA replication enzyme complex and act as direct inhibitors of bacterial DNA synthesis. Therefore, fluoroquinolones exhibit bactericidal properties by causing bacterial DNA damage and rapid bacterial cell death.[1] With the increasing prevalence of drug-resistant infections, the prescription of quinolones seems to be a good choice in children; however, they are rarely used in the pediatric population. There is a concern regarding the potential toxicity of quinolones during chondrogenesis, which is based on animal studies conducted in the 1970s that demonstrated damage to articular cartilage in the weight-bearing joints of young beagle dogs exposed to high doses of quinolones.[2] As these findings were demonstrated only in animal models and there are physiological differences between humans and animals, investigating the adverse effects of quinolones on the bones and cartilage of children is required. This study was performed to systematically analyze the prescription of quinolone antibiotics to children to evaluate whether there was a difference between the risk associated with adverse musculoskeletal events with fluoroquinolone and non-fluoroquinolone antibiotic use.

2. Methods

2.1. Search strategy

The meta-analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analysis criteria. Cochrane Library, Embase, and PubMed databases were searched

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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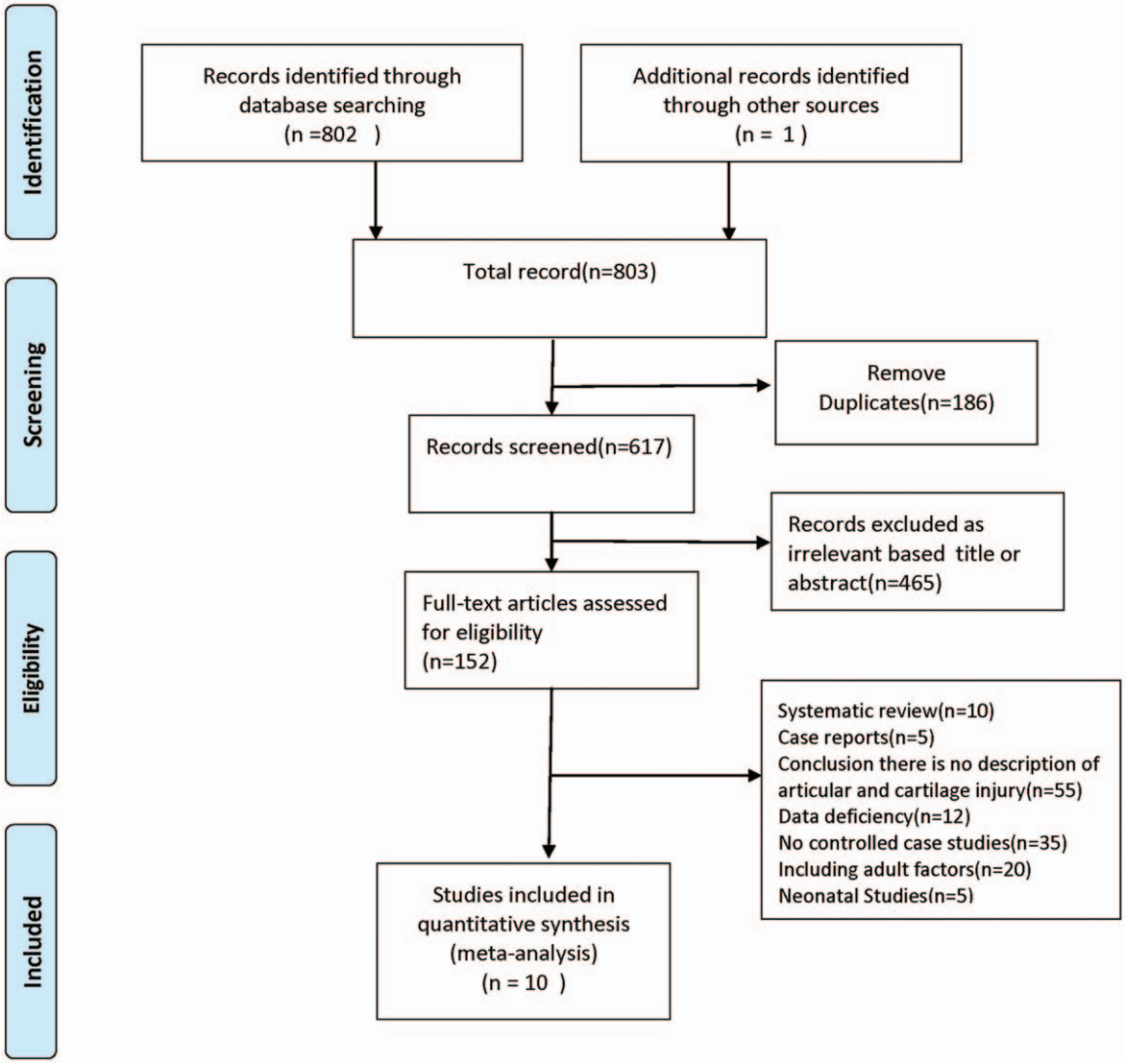

Figure 1. The flowchart of study selection.

for relevant published articles until June 1, 2019. The search terms included "quinolones," "fluoroquinolones," "ciprofloxacin," "fleroxacin," "enoxacin," "enrofloxacin," "gatifloxacin," "gemifloxacin," "moxifloxacin," "norfloxacin," "ofloxacin," "levofloxacin," "pefloxacin," "children," "child," "kid," "RCT (randomized controlled trial)," and "randomized controlled trial". There were no restrictions on language or country, and an expanded search for the included studies was performed.

2.2. The following search sequence was performed in PubMed

- 1 (Fluoroquinolones [mh]) "quinolones) or ciprofloxacin) or fleroxacin) or enoxacin) or enrofloxacin) or gatifloxacin) or gemifloxacin) or moxifloxacin) or norfloxacin) or ofloxacin) or levofloxacin) or pefloxacin"
- 2"RCT or randomized controlled trial"
- 3 (children) or child or kid
- #1, #2, and #3.

2.3. The inclusion criteria were as follows

1. Type of participants; the studies was children, and age was defined as ranging 0 to 18 years old; the criteria was not limited by sex, race, disease type, or region. The criteria were not limited by sex, race, disease type, or region.
2. Type of intervention: the source of conventional treatment, dosage form, dosage approach, and dose were clear for the quinolone group, whereas the non-quinolone group received only conventional treatment without any quinolone antibiotics.
3. Outcomes: suffering from musculoskeletal adverse events: joint pain, joint swelling, reduced movement of joint or radiographic evidence of joint damage, and any other musculoskeletal adverse event.
4. Research type: RCT, case-control, cohort study.

2.4. The exclusion criterion was as follows

(1) study subjects were adults or newborns;

Table 1

Characteristics of the included studies.

'Reference' or 'Source'	Publication year	Quinolone group		Non-quinolone group		Complication type	Quinolone drugs	Non-quinolone drugs	Follow-up time	Treatment type
		Number of patients	Number of non-patients	Number of patients	Number of non-patients					
FDA2004[4]	USA	31	304	21	328	Arthropathy	Ciprofloxacin	Cefixime	6 wk	Complicated urinary tract infections (including pyelonephritis)
FDA2004[4]	USA	46	289	33	316	Arthropathy	Ciprofloxacin	Cefixime	1 yr	Complicated urinary tract infections (including pyelonephritis)
Mohammed Abdus Salam,1998[5]	Bangladesh	13	58	16	56	Arthropathy	Ciprofloxacin	Pivamdinocillin	6 mo	Shigellosis in children
Leibovitz 2000[6]	USA	1	94	1	106	Arthropathy	Ciprofloxacin	Ceftriaxone sodium	4 wk	Acute aggressive diarrhea
Xavier SáEz-Llorens 2002[7]	S Africa	1	161	6	143	Arthropathy	Trovafloxacin	Ceftriaxone	5–7 wk	Bacterial meningitis in children
Xavier SáEz-Llorens 2002	S Africa	1	149	3	131	Joint deformities	Trovafloxacin	Ceftriaxone	5–7 wk	Bacterial meningitis in children
Chuen L. Yee 2002[8]	USA	34	1871	413	19870	Tendon-joint disorder	Ofloxacin	Azithromycin	60 d	-
Chuen L. Yee	USA	1	37	413	19870	Tendon-joint disorder	Levofloxacin	Azithromycin	60 d	-
Chuen L. Yee	USA	128	5776	413	19870	Tendon-joint disorder	Ciprofloxacin	Azithromycin	60 d	-
Chuen L. Yee	USA	30	1580	310	14955	Tendon-joint disorder	Ofloxacin	Azithromycin	60 d	-
Chuen L. Yee	USA	0	16	310	14955	Tendon-joint disorder	Levofloxacin	Azithromycin	60 d	-
Chuen L. Yee	USA	103	4494	310	14955	Tendon-joint disorder	Ciprofloxacin	Azithromycin	60 d	-
Martin Chalumea 2003[9]	France	10	254	1	236	Musculoskeletal diseases	Fluoroquinolone	Amoxicillin	15 d	-
Xavier Sáez-Llorens 2005[10]	Mexico, USA	6	271	2	134	Arthralgia	Gatifloxacin	Amoxicillin	5–7 wk 6–12 mo	Recurrent and nonreactive otitis media in children
Lawrence Sher 2005[11]	USA, Costa rica	1	175	2	171	Arthralgia	Gatifloxacin	Amoxicillin	30 d	Recurrent and nonreactive otitis media in children
Gary J. Noel 2007[12]	USA	28	1312	8	885	Musculoskeletal diseases	Levofloxacin	Non-quinolone antibiotics	2mo	
Gary J. Noel 2007[12]	USA	46	1294	16	877	Musculoskeletal diseases	Levofloxacin	Non-quinolone antibiotics	1 yr	-
John S. Bradley 2007[13]	Argentina	19	514	6	173	Arthralgia, myalgia	Levofloxacin	Amoxicillin-clavulanate potassium	5 wk	Community acquired pneumonia in children

Table 2

The Newcastle-Ottawa Scale (NOS) for assessing the quality of studies included into present meta-analyses.

The Newcastle-Ottawa Scale (NOS)

We downloaded the following scale from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, to evaluate the included studies qualities. The studies that met at least five NOS criteria were considered to be high quality studies.

1. Newcastle-Ottawa Quality Assessment Scale: case control/cross- sectional studies

Note: A study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be given for comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation*
   b) yes, for example, record linkage or based on self reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases*
   b) potential for selection biases or not stated
3) Selection of controls
   a) community controls*
   b) hospital controls
   c) no description
4) Definition of controls
   a) no history of disease (endpoint)*
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.)*
   b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (e.g. surgical records)*
   b) structured interview where blind to case/control status*
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes*
   b) no
3) Non-response rate
   a) same rate for both groups*
   b) non respondents described
   c) rate different and no designation

2. Newcastle-Ottawa Quality Assessment Scale: cohort studies

Note: A study can be awarded a maximum of 1 star for each numbered item within the selection and outcome categories. A maximum of 2 stars can be given for comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____(describe) in the community*
   b) somewhat representative of the average _____in the community*
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort*
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records)*
   b) structured interview
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes*
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor)*

(*continued*)

Table 2

(continued).

The Newcastle-Ottawa Scale (NOS)
b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment*
b) record linkage
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) Yes (select an adequate follow up period for outcome of interest)*
b) No
3) Adequacy of follow up of cohorts
a) Complete follow up - all subjects accounted for*
b) Subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost)*
c) Follow up rate < ____% (select an adequate %) and no description of those lost
d) No statement

(2) no control group was found in the literature;
(3) conference papers, case reports, or review articles;
(4) insufficient original data provided;
(5) side effects did not mention musculoskeletal adverse events.

2.5. Data extraction and quality evaluation and bias risk assessment

Two researchers extracted data independently (without using any tools) from all eligible studies. The quality of the studies was evaluated by 2 reviewers, and a third researcher assessed the study when there was a difference in opinion. The following data were extracted: name of the first author, research site, year of publication, type of complications, drugs used in the quinolone and non-quinolone groups, disease types, and follow-up duration.

The quality of included studies was assessed using the Cochrane template for randomized controlled trials or the The Newcastle–Ottawa Scale[3] template for non-randomized controlled trials. The full criteria for grading has been provided online in the supplementary file: Newcastle-Ottawa Scale, http://links.lww.com/MD/E728. It has 3 categories (selection, comparability, and exposure) and 8 items. Two researchers performed quality assessments individually. In the selection category (adequate definition of the cases, representativeness of the cases, selection of non-quinolones, and definition of non-quinolones) and exposure category (ascertainment of exposure, same method of ascertainment for cases and non-quinolones, and non-response rate), a quality research item received 1 star, and a comparable category (comparability of cases and non-quinolones on the basis of the design or analysis) could receive at most 2 stars. The quality assessment values ranged from 0 to 9 stars. Each band indicates the percentage of the included studies that met each of these quality criteria. A higher score represented better methodological quality. We regarded scores of 0 to 3, 4 to 6, and 7 to 9 as reflecting low, moderate, and high quality, respectively. This scale was a risk of bias assessment tool for observational studies, especially case-control or cohort studies. It was recommended by the Cochrane Collaboration. However, this assessment tool was lack of methodological details in published studies, which may potentially deviate the risk of bias assessment.

2.6. Statistical analysis

Stata 11 software was used for data processing and analysis. The risk ratio (RR) and 95% confidence interval (CI) were calculated to determine the effect size for dichotomous variables. The mean difference and 95% CI were used to calculate the effect size for continuous variables. Heterogeneity tests were assessed using I^2 and Q statistics, and $I^2 > 50\%$ was considered for the existence of heterogeneity among the studies. The data were analyzed using the random-effects model. Publication bias was evaluated by the rank sum test and a funnel chart.

2.7. Ethical statement

This study was carried out in accordance with the recommendations and in the preferred reporting items for systematic reviews and meta-analyses guidelines. Hence, permission from the ethics committee or the institutional review board is not required.

3. Results

3.1. Study selection

A total of 802 articles were screened through e Cochrane Library, Embase, and PubMed, and 1 article was obtained from another source. After eliminating duplicate literature, 617 potentially relevant articles remained. After a second round of screening of titles and abstracts based on the exclusion criteria, 152 articles remained for further evaluation. Ten articles were included after screening,[4–13] as shown in Figure 1. Only 1 of the included articles was a historical cohort study,[8] and the rest were prospective cohort studies. The characteristics of the included studies are shown in Table 1. According to the Newcastle–Ottawa scale, the quality of all studies were > 5 points (Table 2):

Stata 11 software was used for meta-analysis. I^2 and Q tests were used to test heterogeneity. I^2 was found to be 26.7% ($P = .143$). We used a random effects model for Meta-analysis. There were no statistically significant differences between fluoroquinolone and non- fluoroquinolone groups (RR = 1.145, 95% CI = 0.974–1.345, $P = .101$) in terms of bone and muscle damage (Fig. 2).

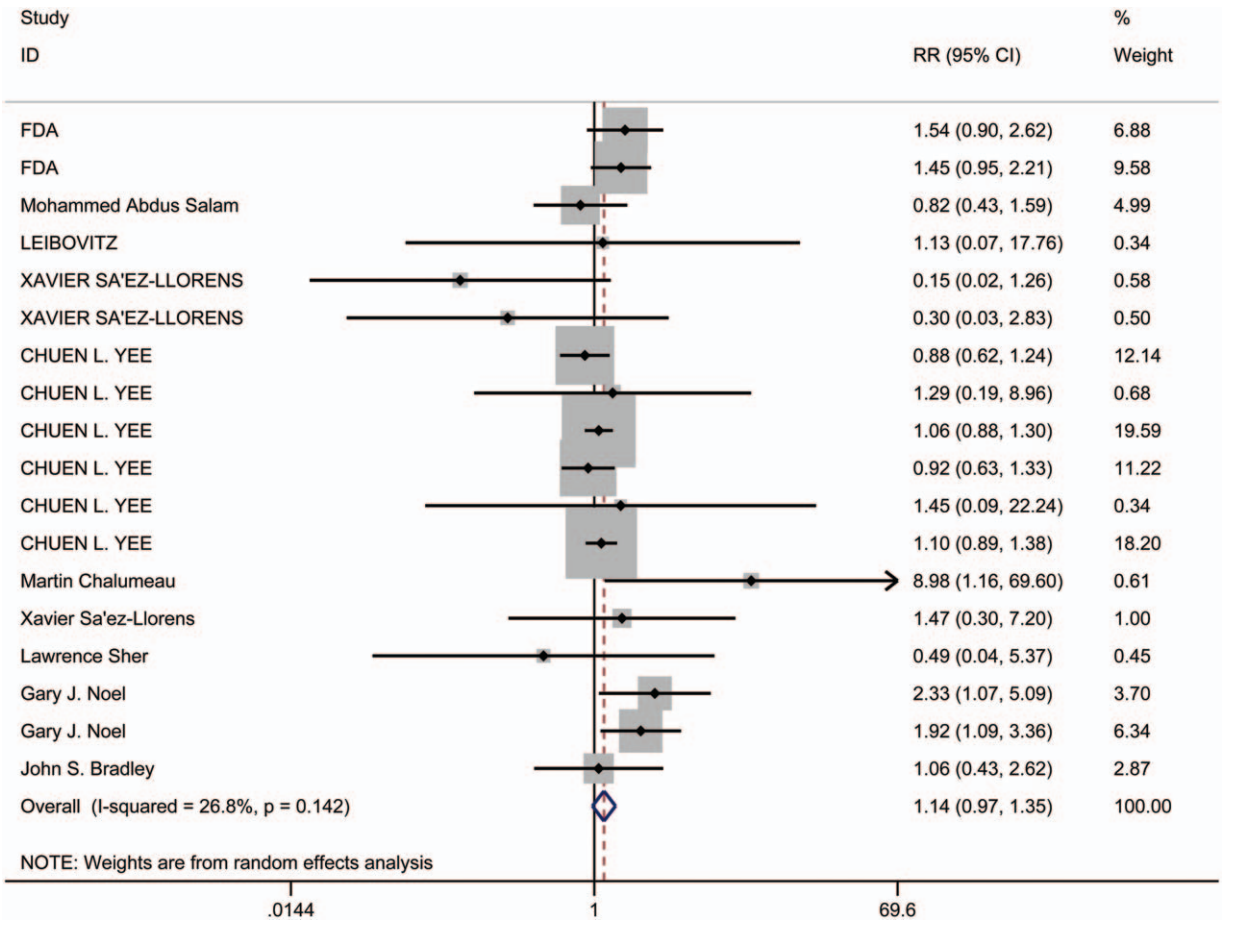

Figure 2. Forest plot of the between fluoroquinolone and non-fluoroquinolone groups in terms of bone and muscle damage.

3.2. Subgroup analysis based on different quinolones

Two statistical methods, I^2 statistics and Q, were used to test heterogeneity. We observed an absence of any heterogeneity, and the random-effects model was used. Meta-analysis showed that the trovafloxacin and levofloxacin subgroups were significantly different from the control group. (Table 3; Fig. 3).

3.3. Sensitivity analysis

To test the stability and reliability of the results, a sensitivity analysis was performed. The results showed that removing individual studies did not have any significant effect on the combined effect size RR value, indicating that the results were stable and reliable (Fig. 4).

3.4. Publication bias

To check for publication bias, a funnel plot was constructed, and Egger test was performed. The funnel plot showed a roughly symmetrical distribution and the Egger test *P* value was .688 (95% CI:−0.7348835–1.086832), indicating that there was no publication bias (Fig. 5).

4. Discussion

Although fluoroquinolones are routinely used to treat common infections such as adult urinary tract infections and pneumonia, its use in the pediatric population is limited due to concerns about significant adverse effects. In a systematic review, Adefurin et al[14] reported 1065 cases of adverse events among 16,184

Table 3

Subgroup analysis among the different quinolones.

Drug	Number of studies	Heterogeneity		Method	RR	95% CI	*P*
		I^2	*P*				
Ciprofloxacin	6	0.0%	.559	Random	1.125	0.986, 1.282	.079
Trovafloxacin	2	0.0%	.673	Random	0.209	0.045, 0.972	.046
Ofloxacin	2	0.0%	.860	Random	0.895	0.695, 1.154	.393
Levofloxacin	5	0.0%	.754	Random	1.761	1.187, 2.612	.005
Gatifloxacin	2	0.0%	.454	Random	1.053	0.281, 3.951	.939

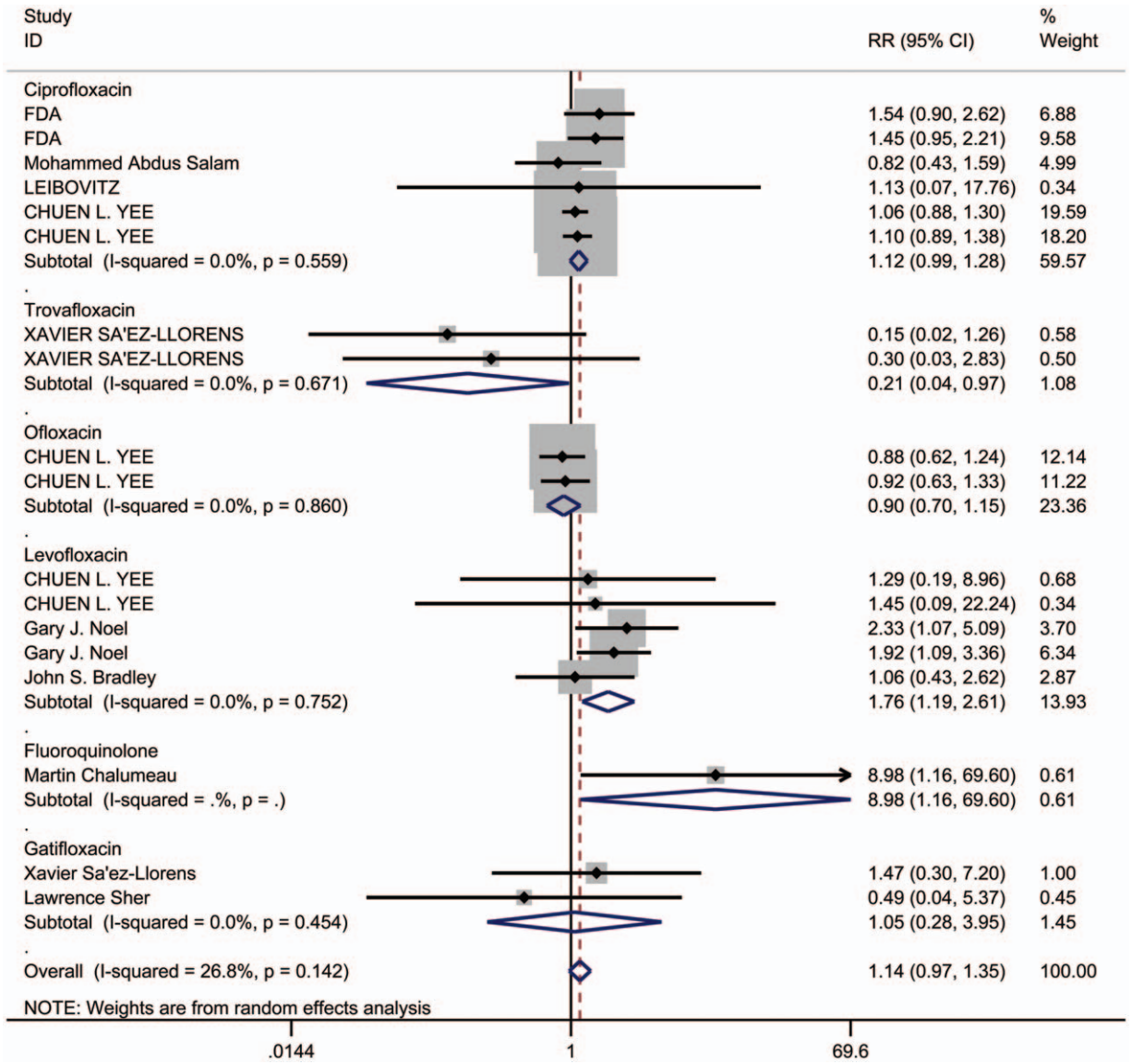

Figure 3. Forest plot of the subgroup different quinolones.

pediatric patients on ciprofloxacin therapy (7% risk; 95%, CI 3.2–14.0%). The adverse event was musculoskeletal, which was significantly higher in the fluoroquinolone group than in the non-fluoroquinolone group, although all joint injuries were reversible. Data on the safety of fluoroquinolones in children are still limited, and safety issues have led to the termination of research with fluoroquinolones in the pediatric population during clinical development. Therefore, several fluoroquinolones have been withdrawn from the US market, including temafloxacin, trovafloxacin, and gatifloxacin.[15] The most common adverse effects of fluoroquinolones in adults are gastrointestinal symptoms (nausea, vomiting, and diarrhea), severe allergic skin reactions, and central nervous system effects such as dizziness, headache, and anxiety.[16] In August 2013, the FDA requested that all fluoroquinolones be updated with labels and drug guidelines to better describe the severe adverse effects of peripheral neuropathy. A review of the adverse event reporting system database shows that the onset of peripheral neuropathy with fluoroquinolones is fast and can be severe, disabling, and permanent. Unfortunately, there are no clinical predictors to identify the population at risk.[17] Animal toxicity studies have shown that young beagle dogs experience joint toxicity in weight-bearing joints after receiving a first-generation quinolone, namely piperic acid. Since then, all quinolones have resulted in adverse effects on joints in juvenile animals,[2] and the extent of adverse drug reactions varies according to drug and animal species. Of all animals studied, dogs are most sensitive to joint toxicity caused by fluoroquinolones.[18]

Chalumeau et al conducted a multicentric, observational, comparative cohort study in France from 1998 to 2000 based on 276 fluoroquinolone-treated pediatric patients and 249 cases treated with other antibiotics for different kinds of infections (respiratory infection and pneumonia, intestinal infection, sepsis and meningitis, urinary tract infection, and prevention of neutropenia).[9] Compared to that in the non-quinolone-treated group, musculoskeletal adverse events were more prevalent in the

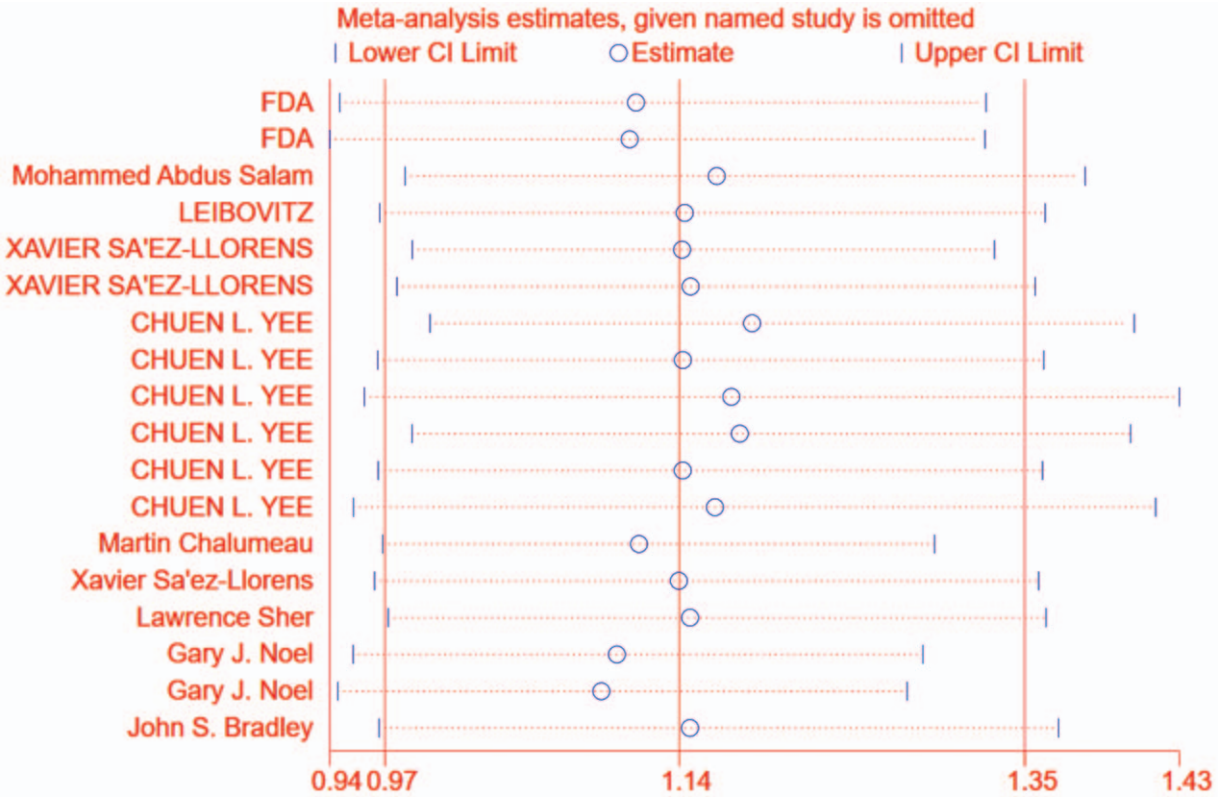

Figure 4. Sensitivity analysis plots: to test the stability and reliability of the results.

quinolone-treated group (3.8% vs 0.4%), and no severe or sustained musculoskeletal damage was found after a single follow-up. Further, Noel et al[12] evaluated the safety and tolerability of levofloxacin based on 2523 children (a total of 2233 children completed 1-year follow-up, including 1340 in the levofloxacin treatment group and 893 in the control group, aged 6 months–16 years). The results showed that the incidence of skeletal muscle adverse events in the levofloxacin treatment group was higher than that in the non-quinolone control group. Moreover, the incidences of skeletal muscle adverse events in the 2-month follow-up and control groups were 2.1% and 0.9% ($P=.04$), respectively, and the incidences of adverse reactions were 3.4% and 1.8% ($P=.03$). Bradley et al[28] conducted a 5-year long-term follow-up of 207 children with adverse skeletal muscle reactions (124 of them from the levofloxacin treatment group and 83 from the non-quinolone treatment group). At the end of the 5-year follow-up, only 2 children (1 in each of the 2 groups) had skeletal muscle adverse events that might have been caused by drug therapy. The data safety and monitoring committee concluded that neither of the 2 adverse events was "possibly related" to the study drug.

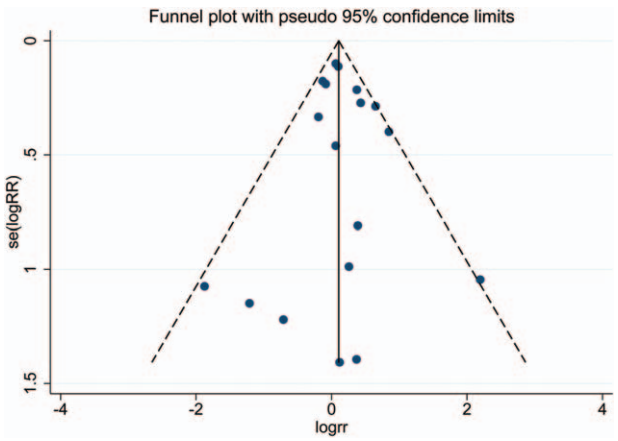

Figure 5. Begg funnel plot testing possible publication bias.

Animal studies have shown that joint disease occurs earlier in young animals. However, a neonatal matched case-control study found that ciprofloxacin does not affect chondrogenesis. Thirty neonates with multidrug-resistant sepsis were treated with intravenous ciprofloxacin for 14 days and 30 matched neonates with sepsis were treated with non-quinolone antibiotics. There were no significant differences in mean serum electrolyte, liver, kidney, and hematological parameters between the 2 groups. Continuous ultrasound examinations of the knee cartilage after 1 and 6 months showed no difference between the 2 groups.[19] In addition, a systematic review by Kaguelidou et al on newborns found no serious adverse events, particularly joint toxicity, with ciprofloxacin.[20] A single-center observational cohort study in Australia revealed that levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia can reduce the risk of infection by 70%.[21] Further, for the treatment and prevention of multidrug-resistant tuberculosis in children, quinolone antibiotics have achieved good benefits and have been used for a long time without reports of severe articular cartilage damage.[22,23] Therefore, in a statement in 2011, the American

Academy of Pediatrics concluded that "fluoroquinolones are quite safe in children" and outlined the rationale for their use.[24]

Despite this available evidence, the perception of risk with fluoroquinolone remains high. Arthrodynia is the most common arthropathic symptom in children (50%), which mainly affects the knee joint. Tendon or joint disease and reduced movement also account for a large proportion of joint disease cases (19% and 15%, respectively).However, these musculoskeletal events are reversible with management.[25] In 2016, the American Academy of Pediatrics recommended that fluoroquinolones can be used for the following infections in children:[26]

1. exposure to anthrax *Bacillus* (also approved by the FDA);
2. urinary tract infection caused by *Pseudomonas aeruginosa* or other multidrug-resistant gram-negative bacilli (FDA-approved for treatment of complicated urinary tract infections and pyelonephritis caused by *Escherichia coli*);
3. chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa*;
4. acute or chronic osteomyelitis caused by *P. aeruginosa*;
5. deterioration of pulmonary functions in patients with cystic fibrosis colonized by *P. aeruginosa*;
6. infection caused by susceptible mycobacteria;
7. gram-negative bacilli infection in immunosuppressed patients resistant to other alternative antibacterial agents;
8. gastrointestinal infections caused by a variety of resistant species such as *Shigella*, *Salmonella*, *Vibrio cholerae*, or *Campylobacter*;
9. severe infections in children with a history of severe allergies to conventional antibacterial agents.

This study showed that fluoroquinolones have no differential effect on musculoskeletal adverse events when compared to that with other antibiotics. Therefore, restricting fluoroquinolones in children should not be recommended, although a low risk of fluoroquinolone-induced joint damage cannot be excluded. A study investigating 657,950 cases of adult patients found that quinolones are indeed a risk factor for tendon rupture.[27] Hence, it is advisable to use fluoroquinolones in children with life-threatening diseases where other antibiotics are considered ineffective. Specific recommendations made by the American Academy of Pediatrics, 2016, on the use of fluoroquinolones in children can thus be followed.[26]

There are some limitations to this study. Among the 10 included studies, 1 was a retrospective study,[8] in which adjustment for multivariate analysis was not performed; therefore, the potential side effects of quinolones might have been ignored or underestimated in this study. In addition, the included studies are relatively old, and there is a lack of relevant randomized controlled trials in recent years. In addition, most of the studies had a short follow-up period (several weeks–1 year). Therefore, large-scale prospective studies in children and adults with a considerably longer follow-up duration are warranted.

In conclusion, this meta-analysis revealed that there was no difference in the adverse musculoskeletal events caused by fluoroquinolone and non-quinolone antibiotics. Fluoroquinolone antibiotics may be appropriate for use in children when other antibiotics prove ineffective.

Author contributions

Ji-gan Wang and Hai-Rong Cui conceived and designed the study. Ji-gan Wang and Hua-Bo Tang searched the literature and extracted data. Yi-sen Hu performed statistical analyses. All authors wrote and reviewed the manuscript.

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Investigation: Ji-gan Wang, Yi-sen Hu.
Resources: Hua-Bo Tang.
Software: Hai-Rong Cui, Yi-sen Hu.
Writing – original draft: Ji-gan Wang, Hai-Rong Cui, Hua-Bo Tang.
Writing – review & editing: Ji-gan Wang.

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