ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΕΡΓΑΣΤΗΡΙΟ ΒΙΟΜΑΘΗΜΑΤΙΚΩΝ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΜΕΘΟΔΟΛΟΓΙΑ ΤΗΣ ΒΙΟΪΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ,

ΒΙΟΣΤΑΤΙΣΤΙΚΗ ΚΑΙ ΚΛΙΝΙΚΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗ »

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ ΜΕ ΘΕΜΑ

«Assessment of the reporting quality of Randomized Controlled Trials and Observational Studies for paracetamol in the treatment of patent ductus arteriosus from 2011 to 2018»

«Εκτίμηση της ποιότητας αναφοράς των τυχαιοποιημένων κλινικών μελετών και μελετών παρατήρησης που αφορούν στην χρήση παρακεταμόλης στην αντιμετώπιση του Ανοιχτού Βοταλείου Πόρου από το 2011 μέχρι το 2018»

ΤΗΣ ΦΟΙΤΗΤΡΙΑΣ

ΓΟΥΔΕΣΙΔΟΥ ΜΑΡΙΑΣ

2017-2018

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

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CONTENTS

ABSTRACT

INTRODUCTION : Randomized Controlled Trials (RCTs) are considered to be the best among all clinical studies for the evaluation of clinical interventions. However, much of the medical knowledge comes from Observational Studies (OS). The CONSORT (Consolidated Standards of Reporting Trials) statement is a checklist published in 1996, aiming to improve the quality of RCTs. The STROBE (Strengthening the reporting of Observational studies in Epidemiology) statement is published in 2007 to improve the quality of OS.

AIM OF THE STUDY : The aim of this study is to assess published RCTs and OS, concerning the use of Paracetamol (or Acetaminophen) as an alternative therapeutic approach in the treatment of Patent Ductus Arteriosus (PDA) in preterm neonates.

METHODS : PubMed was searched for English-language RCTs and OS about the use of Paracetamol in the treatment of PDA. All RCTs comparing the effectiveness and safety of paracetamol to those of indomethacin and ibuprofen which are used as a first choice drug in PDA in preterm neonates, or of a placebo, were eligible. They were assessed using the 25-item CONSORT checklist of 2010. All OS were eligible and they were assessed using the 22-item STROBE checklist of 2007.

RESULTS : The search identified nine eligible articles for RCTs and 22 eligible articles for OS. Only 2 of the 9 RCTs had a CONSORT adherence of > 75 % and 7 of the 22 OS a STROBE adherence > 75 %.

CONCLUSIONS : Quality of reporting in RCTs and OS on paracetamol for treatment of PDA is unsatisfactory. Further improvement is needed.

KEY WORDS : CONSORT, Randomized Controlled Trials, STROBE, Observational Studies, Quality, Paracetamol, Patent Ductus Arteriosus.

ΠΕΡΙΛΗΨΗ

ΕΙΣΑΓΩΓΗ : Οι Τυχαιοποιημένες Κλινικές Μελέτες (ΤΚΜ) θεωρούνται οι καλύτερες κλινικές μελέτες για την αξιολόγηση των κλινικών παρεμβάσεων. Όμως μεγάλο μέρος της ιατρικής γνώσης προέρχεται από τις μελέτες παρατήρησης (ΜΠ). Η δήλωση CONSORT (Ενισχυμένα Πρότυπα Αναφοράς Δοκιμών) είναι ένας Κατάλογος Στοιχείων που δημοσιεύτηκε το 1996, με σκοπό να βελτιώσει την ποιότητα των ΤΚΜ. Η δήλωση STROBE (Ενδυνάμωση της Αναφοράς στις Μελέτες Παρατήρησης στην Επιδημιολογία) δημοσιεύτηκε το 2007 με σκοπό να βελτιώσει τις ΜΠ.

ΣΤΟΧΟΙ : Σκοπός αυτής της μελέτης είναι να εκτιμήσει την ποιότητα αναφοράς των δημοσιευμένων ΤΚΜ και ΜΠ που αφορούν στη χρήση παρακεταμόλης (ή ακεταμινοφαίνης) ως εναλλακτικής θεραπευτικής

προσέγγισης στη θεραπεία του Ανοιχτού Βοταλλείου Πόρου (ΑΒΠ) στα πρόωρα νεογνά.

ΜΕΘΟΔΟΙ : Διερευνήθηκε το PubMed για ΤΚΜ στην αγγλική γλώσσα που αφορούσαν στη χρήση της παρακεταμόλης στην θεραπεία του ΑΒΠ. Επιλέχτηκαν όλες οι ΤΚΜ που συνέκριναν την αποτελεσματικότητα και την ασφάλεια της παρακεταμόλης έναντι εκείνων της ινδομεθακίνης, της ιβουπροφένης, ή ενός εικονικού φαρμάκου. Η ποιότητα αναφοράς αξιολογήθηκε με βάση τον κατάλογο στοιχείων CONSORT του 2010. Επιλέχθηκαν όλες οι ΜΠ και αξιολογήθηκαν με βάση τον κατάλογο στοιχείων STROBE του 2007.

ΑΠΟΤΕΛΕΣΜΑΤΑ : Η έρευνα ανέδειξε 9 άρθρα για ΤΚΜ και 22 για ΜΠ. Μόνο 2 από τις 9 ΤΚΜ και 7 από τις 22 ΜΠ παρουσιάζουν βαθμό εναρμόνισης > 75 % με τα στοιχεία της λίστας CONSORT και της λίστας STROBE αντίστοιχα.

ΣΥΜΠΕΡΑΣΜΑΤΑ : Η ποιότητα των ΤΚΜ και ΜΠ για την παρακεταμόλη στη θεραπεία του ΑΒΠ δεν είναι ικανοποιητική. Απαιτείται περαιτέρω βελτίωση.

ΛΕΞΕΙΣ-ΚΛΕΙΔΙΑ : CONSORT, Τυχαιοποιημένες Κλινικές Μελέτες, STROBE, Μελέτες Παρατήρησης, Ποιότητα, Παρακεταμόλη, Ανοιχτός Βοτάλλειος Πόρος

INTRODUCTION

A persistent patent ductus arteriosus (PDA) is a common complication of prematurity and respiratory distress syndrome (RDS) in preterm neonates. Its incidence rate may come up to 64% of infants born at 27 to 28 weeks' gestation and 87% of infants born at 24 weeks, at 7 days of age.[1] The ductus arteriosus is a blood vessel that connects the pulmonary artery to the aorta during fetal life so that blood bypasses the non-functioning fetal lungs. After birth it closes so that non-oxygenated blood is driven from pulmonary artery to the lungs and oxygenated blood is driven from the aorta to the systemic circulation. In the case that DA remains open or re-opens after initially closed after birth, it has significant sequences deteriorating the clinical status and affecting the survival rate of preterm neonates.[2,3] As it becomes hemodynamically significant (hsPDA), a left to right shunting starts through the open ductus and despite the ability of the left ventricle to increase its output, blood flow distribution to vital organs is altered. The haemodynamic instability caused by the shunt has gastrointestinal, cerebral and renal effects including necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), decreased kidney function and bronchopulmonary dysplasia (BPD) and if not treated may even lead to death.

There are 3 therapeutical approaches for the treatment of hsPDA:

1.Conservative approach

2. Pharmacological approach and

3. Surgical approach.

Non-steroid Anti-inflammatory Drugs (NSAIDS) and specifically indomethacin and ibuprofen are the first choise drugs implemented in the treatment of hsPDA. The reported treatment success is between 70% - 85 %.[4] By inhibiting the cyclo-oxygenase (COX) component of prostaglandin-H2 synthase (PGHS), these two drugs reduce the levels of prostaglandins, on which depends the persistency of ductus arteriosus. However these drugs may have serious adverse effects like renal failure, gastrointestinal perforation and bleeding, peripheral vasoconstriction and decreased platelet aggregation.

Very recently paracetamol (acetaminophen), an inhibitor of the peroxidase component of prostaglandin-H2 synthetase has been considered as an alternative drug for the treatment of infants with contraindications to NSAIDS.[5] In the literature there is evidence that paracetamol may be as effective as the previously used drugs with less adverse effects.[7-15] However, many aspects of paracetamol use for ductal closure in preterm neonates, such as efficacy in extremely preterm and low birthweight infants, safety profile, optimal dose, route of administration and timing of first dose remain unexplored.[6]

Well designed RCTs are the most reliable research method to establish the effectiveness of new healthcare interventions, minimizing biased results leading to incorrect treatment decisions in health care at all levels. It is important for health care providers to be able to assess the quality of the methods used in the published RCTs in order to assess their strengths and limitations.

A group of scientists and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statement in order to improve the quality of reporting of RCTs. It was first published in 1996 and updated in 2001. The CONSORT Statement is an evidence-based minimum set of recommendations including a checklist and flow diagram for reporting RCTs and is intended to facilitate the complete and transparent reporting of trials and aid their critical appraisal and interpretation[16]. However, the CONSORT statement should not be used as a quality appraisal tool but rather as a guide for reporting of RCTs[17]. The objective of CONSORT is to provide guidance to authors about how to improve the reporting of their trials. Trial reports need be clear, complete, and transparent

Many leading medical journals and major international editorial groups have endorsed the CONSORT statement in order to improve the quality of their publications. The introduction of CONSORT within journals is associated with improved quality of reports of RCTs.

After an expert meeting in January 2007, the CONSORT statement has been further revised and is published as the CONSORT 2010 Statement.

The CONSORT statement 2010 will be used in this study to evaluate the published RCTs concerning the effectiveness and safety of Paracetamol in the treatment of PDA[18].

The STROBE Statement consists of a checklist of 22 items, which relate to the title, abstract, introduction, methods, results, and discussion sections of articles. The STROBE Statement provides guidance to authors about how to improve the reporting of observational studies and facilitates critical appraisal and interpretation of studies by reviewers, journal editors, and readers. The STROBE statement 2007 will be used in this study to evaluate published OS concerning the use of paracetamol for the closure of PDA in preterm neonates.[22]

METHODS

Data sources and search strategies

We searched PubMed for RCTs concerning the use of paracetamol in the treatment of PDA in preterm neonates. We used as filter the "Randomized Controlled Trial" type of article and we set no time limitation. We used as a search criterion the words Paracetamol or Acetaminophen (synonymes) and Patent Ductus Arteriosus. Because of the small number of RCTs retrieved (N = 9) we removed the filter "Randomized Controlled Trial", repeated the search and all articles found were also reviewed. All observational studies retrieved (N = 22) were included in a separate quality of reporting assessment study. Finally we searched the references of the articles retrieved.

Selection criteria

We included RCTs in which paracetamol was compared to placebo or other drugs used for closure of PDA (indomethacin, ibuprofen) irrespective of dose, duration and mode of administration in preterm infants. Trials were eligible if they had randomly assigned participants to two or three treatment arms since paracetamol may be compared to indomethacin, ibuprofen or both, or to placebo. In the included studies paracetamol has been used either prophylactically or therapeutically. For the observational studies the use of paracetamol for closure of a patent ductus arteriosus in preterm infants was the selection criterion irrespective of dose, duration and mode of administration.

Reporting assessment tool

The CONSORT statement 2010 was the tool of evaluation of the reporting quality of the trials. The CONSORT 2010 checklist includes 25 main categories and 12 subcategories organized in sections: Title and abstract, Introduction, Methods, Results, Discussion and Other information. (Figure 1) We calculated the percentage of compliance to the CONSORT checklist items taking into account the total 37 items. The CONSORT explanation and elaboration document was used as a guideline for the assessment.[18]

FIGURE 1 : CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	

	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

For the observational studies the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist was used for the assessment of the studies[22].(Figure 2)

FIGURE 2 : STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total

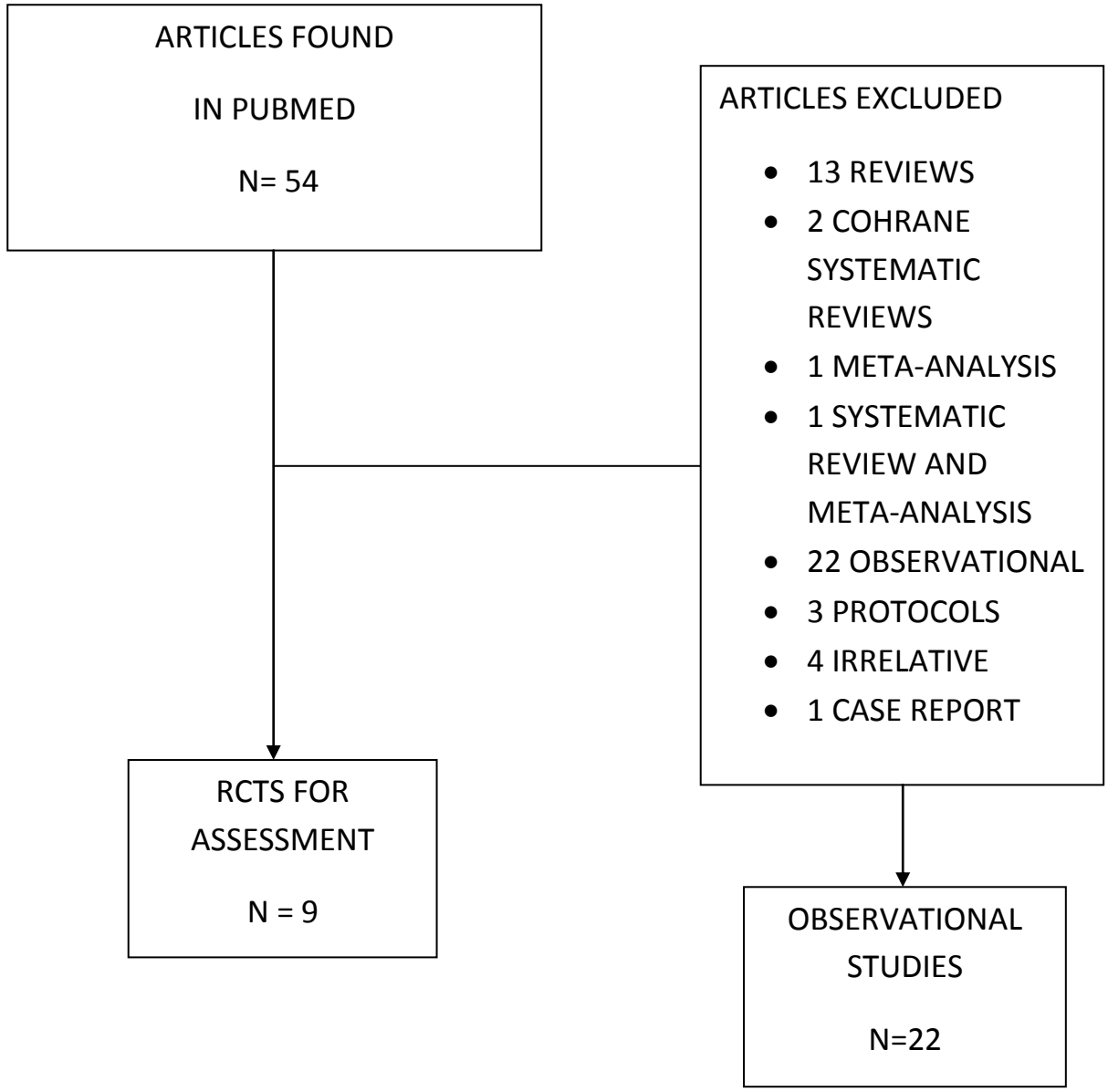
		amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

RESULTS

Nine studies were included in the CONSORT study that reported on the whole on one thousand and four infants (1004). One study compared paracetamol to both ibuprofen and indomethacin[12]. Six studies compared treatment of PDA with paracetamol versus ibuprofen [7,8,11,13-15] enrolling 579 infants. One study compared paracetamol to indomethacin[9] and one to placebo[10]. One more RCT was found (author Asbagh,2015), not in the PubMed search but in the Cochrane Collaboration Review article about the use of paracetamol for PDA in preterm or low birth weight infants published in 2018 [19] but, the abstract excluded, the article was written in the Farci language and no detailed data could be extracted. Two more studies were excluded[20,21] since they were protocols.

Twenty-two studies were included in the STROBE study that reported on a total population of four hundred thirty-seven preterm neonates (437).

FIGURE 3 PUBMED SEARCH FLOW DIAGRAM



Clinical characteristics, treatment protocols and publication details of the RCTs are gathered in table 1.

TABLE 1 : Characteristics of the RCTs

	Author Publication year	Sample size	Birth Weight g	Gestational age weeks	Route	Dose mg/kg/day
1	Dang et al PLoS One, 2013[7]	Paracetamol N=80	1591±348	31.2 ± 1.8	ORAL	60 mg/kg x 3days
		Ibuprofen N=80	1531±453	30.9 ± 2.2		10mg/5mg/5mg /kg/day
2	Oncel et al J Pediatr, 2014[8]	Paracetamol N=45	931±217	27.3 ± 1.7	ORAL	60 mg/kg x 3days
		Ibuprofen N=45	973±224	27.3 ± 2.1		10mg/5mg/5mg /kg/day
3	Dash et al Indian Pediatr, 2015[9]	Paracetamol N=38	989±299	28.5±2.7	ORAL	60 mg/kg x7 days
		Indomethacin N=39	1027±262	28.9±2.6	IV	0.2mg/kg x3 days
4	Harkin et al J Pediatr, 2016[10]	Paracetamol N=23	1220±430	28.4±2.4	IV	Loading dose 20mg/kg, 30 mg/kg x 4 days
		Placebo (0.45% saline solution) N=25	1120±340	28.3±2.1		
5	Bagheri et al Iran J Pediatr, 2016[11]	Acetaminophen N=80	1646.26±59.14	31.53±2.31	ORAL	60 mg/kg x 3days
		Ibuprofen N=80	1642.62±58.46	31.7±2.24		20mg/10mg/10mg /kg/day
6	El-Mashad Eur J Pediatr, 2016[12]	Paracetamol N=100	1100±130	26±1.9	IV	60 mg/kg x 3days
		Ibuprofen N=100	1000±120	25±2.1		10mg/5mg/5mg /kg/day
		Indomethacin N=100	1100±140	26±2.1		0.2mg/kg/12hx3
7	Yang et al Exp Ther med, 2016[13]	Acetaminophen N=44	2219±606	33.6±2.1	ORAL	60 mg/kg x 3days
		Ibuprofen N=43	2091±657	33.4±2.1		10mg/5mg/5mg /kg/day
8	Al-lawama et al J Int Med Res, 2018[14]	Paracetamol N=13	1059±386	28 (23-32)	ORAL	40 mg/kg x 3days
		Ibuprofen N=9	1192±269	28 (25-35)		10mg/10mg/10mg /kg/day
9	El-Farrash J Matern Fetal Neonatal Med, 2018[15]	Paracetamol N=30	1530±560	30.53±1.55	ORAL	60 mg/kg x 3days
		Ibuprofen N=30	1740±470	31.73±1.98		10mg/5mg/5mg /kg/day

Table 2 : Percentage of CONSORT items reported in the article

STUDY	Articles by author	CONSORT ITEMS REPORTED	Percentage of CONSORT items reported
1	Dang et al, 2013[7]	26/37	70 %
2	Oncel et al, 2014[8]	25/37	68 %
3	Dash et al, 2015[9]	28/37	76 %
4	Harkin et al, 2016[10]	30/37	81 %
5	Bagheri et al, 2016[11]	21/37	57 %
6	El-Mashad et al, 2016[12]	23/37	62 %
7	Yang et al, 2016[13]	19/20	51 %
8	Al-lawama et al, 2018[14]	23/37	62 %
9	El-Farrash et al, 2018[15]	25/37	68 %

2 articles had a CONSORT compliance score of > 75 % (22.2 %).

5 articles had a CONSORT compliance score > 65 % (55.5 %).

7 articles had a CONSORT compliance score > 60 % (77.7 %).

9 articles had a CONSORT compliance score > 50 % (100 %).

Studies were published in eight different journals. The impact factors of the journals in comparison with the CONSORT compliance score of the articles published are reported in table 2.

TABLE 3 Impact factors of Journals where the articles were published

JOURNAL NAME	ARTICLES	IMPACT FACTOR	CONSORT SCORE
JOURNAL OF PEDIATRICS	2 4	3.667	70% 84%
PLOS ONE	1	2.766	73%
EUROPEAN JOURNAL OF PEDIATRICS	6	2.242	54%
THE JOURNAL OF MATERNAL FETAL AND NEONATAL MEDICINE	9	1.493	65%
EXPERIMENTAL AND THERAPEUTIC MEDICINE	7	1.41	51%
INDIAN PEDIATRICS	3	1.145	76%
JOURNAL OF INTERNATIONAL MEDICAL RESEARCH	8	1.023	60%
IRANIAN JOURNAL OF PEDIATRICS	5	0.902	57%

Apart from the total compliance score of each article, it is of interest to analyze the frequency of reporting of the 37 items of the CONSORT checklist for the nine articles combined. As all articles were published recently(after 2013), no pre- and post- CONSORT statement compliance difference could be investigated.

The results of this analysis are depicted in table 4 :

TABLE 4

Section/Topic	Item No	Number of articles reporting the item	Percentage of articles reporting the CONSORT item
Title and abstract	1a	6/9	67 %
	1b	7/9	78 %
Introduction			
Background and objectives	2a	9/9	100 %
	2b	9/9	100 %
Methods			
Trial design	3a	6/9	67 %
	3b	0/9	0 %
Participants	4a	9/9	100 %
	4b	9/9	100 %
Interventions	5	9/9	100 %
Outcomes	6a	9/9	100 %
	6b	0/9	0 %
Sample size	7a	9/9	100 %
	7b	0/9	0 %
Randomization:			
Sequence generation	8a	6/9	67 %
	8b	5/9	55 %
Allocation concealment mechanism	9	8/9	89 %
Implementation	10	1/9	11 %
Blinding	11a	7/9	78 %
	11b	1/9	11 %
Statistical methods	12a	9/9	100 %
	12b	3/9	33 %
Results			
Participant flow	13a	7/9	78 %
A diagram is recommended	13b	7/9	78 %

Recruitment	14a	9/9	100 %
	14b	0/9	0 %
Baseline data	15	9/9	100 %
Numbers analysed	16	8/9	89 %
Outcomes and estimation	17a	5/9	55 %
	17b	2/9	22 %
Ancillary analyses	18	5/9	33 %
Harms	19	9/9	100 %
Discussion			
Limitations	20	9/9	100 %
Generalisability	21	8/9	89 %
Interpretation	22	9/9	100 %
Other information			
Registration	23	6/9	67 %
Protocol	24	1/9	11 %
Funding	25	4/9	44 %

From the analysis by CONSORT item it is noted that only 20 out of the 37 items (54 %) are addressed in 75 % or more of the articles published from 2013-2018. Items addressed in 100 % of the articles were background and objectives (2a, 2b), participants (4a, 4b), interventions (5), outcomes (6a), sample size (7a), statistical methods (12a), recruitment (14a), baseline data (15), harms (19), limitations (20) and interpretation (22).

Implemenation (10), additional analyses (12b), outcomes and estimation (17a, 17b), ancillary analyses (18) and protocol (24) were the most underreported items.

Clinical characteristics, treatment protocols and publication details of the Observational studies are gathered in table 5.

TABLE 5 : Characteristics of Observational studies

	Author Publication year	Sample size	Birth Weight Median (min-max), g	Gestational age Median (min-max), days	Postnatal age Median (min-max), days	Route	Dose mg/kg/day
1	Hammerman et al Pediatrics,2011[5]	5	935 (720-1210)	26 (26-29)	10 (3-35)	ORAL	60
2	Oncel et al Arch Dis Child Fetal Neonatal Ed., 2012[23]	8	995 (630-2970)	28 (23-26)	9.5 (5-27)	ORAL	60
3	Oncel et al Neonatology, 2013[24]	10	775 (590-990)	27 (24-29)	6 (2-15)	IV	60
4	Alan et al Neonatology, 2013[25]	3	840 (810-1240)	26 (26-33)	9 (8-19)	IV	60
5	Yurttutan et al J Matern Fetal Neonatal Med, 2013[26]	6	1260 (920-1600)	28 (26-32)	4 (3-7)	ORAL	60
6	Sinha et al J Clin Neonatol, 2013[27]	10	995 (800-1380)	29 (27-33)	5 (4-7)	ORAL	45
7	Jasani et al J Postgrad Med, 2013[28]	6	1107 (1040-1234)	29 (28-31)	5.5 (3-10)	ORAL	60
8	Kessel et al J Matern Fetal Neonatal Med, 2014[29]	7	991 (789-1322)	28 (26-30)	6 (2-27)	ORAL	60
9	Nadir et al J Perinatol, 2014[30]	7	853 (656-951)	26 (24-27)	5 (2-22)	ORAL	60
10	El Khuffash Pediatr Res, 2014[31] (Human study)	21	790 (530-1200)	25 (24-28)	25 (3-56)	9 IV 12 ORAL	60
11	Aikio et al J Matern Fetal Neonatal Med, 2014[32]	102	1201±379	28.5±1.9	8 (3-19.5)	IV	LOADING 20 30
		88	1308±369	29±2.1			

12	Tekgunduz et al Cardiol Young, 2014[33]	13	950 (470-1390)	29 (24-31)	3 (2-9)	IV	30 (1st patient 60)
13	Ozdemir et al Pediatr Cardiol, 2014[34]	7	820 (620-1615)	25 (23-32)	35 (20-47)	ORAL	60
14	Terrin et al Ital J Pediatr, 2014[35]	8	700 (530-930)	26 (23-29)	2 (2-5)	IV	30-60
15	El Khuffash Arch Dis Child Fetal Neonatal Ed, 2015[36]	36	773 (645-954)	26 (24-27)	27 (16-39)	IV	60
16	Roofthooft et al Eur J Pediatr, 2015[37]	33	750 (365-1130)	25 (23-26)	14 (IQR=12)	IV	60
17	Weisz et al J Perinatol,2016[38]	26	700 (633-910)	24.4 (24.3-26)	25 (18-32)	ORAL	60
18	Memisoglou et al J Matern Fetal Neonatal Med, 2016[39]	11	790 (415-1580)	26 (23-30)	3 (1-15)	IV	60
19	Valerio et al Eur J Pediatr, 2016[40] first-line	30	853.3±286.9	26.3±2.4	84 h (48-360)	IV	60
	rescue	18	887.7±297	26.5±2.3	348 h (120-8064)		
20	Luecke et al J Pediatr Pharmacol Ther, 2017[41]	41	760 (614-948)	25 (24-27)	15 (8-19)	88% IV 12% ORAL	60
21	Pharande et al Pediatr Cardiol, 2018[42]	20	724.1±143	25.7±1.5	33.5±15	ORAL	60
22	Tofe et al Front Pediatr, 2018[43]	9	1052 (560-1860)	28 (25-32)	4 (2-35)	IV	60

TABLE 6 : Number of items of STROBE checklist reported and Percentage of STROBE items reported in the article

STUDY	ARTICLES BY AUTHOR, YEAR OF PUBLICATION	STROBE ITEMS REPORTED	PERCENTAGE
1	Hammerman et al, 2011[5]	10/23	43.5 %
2	Oncel et al, 2012[23]	8/23	35 %
3	Oncel et aL, 2013[24]	17/23	74 %
4	Alan et al, 2013[25]	6/23	26 %
5	Yurttutan et al, 2013[26]	12/23	52 %
6	Sinha et al, 2013[27]	8/23	35 %
7	Jasani et al , 2013[28]	10/23	43.5 %
8	Kessel et al, 2014[29]	10/23	43.5 %
9	Nadir et al, 2014[30]	10/23	43.5 %
10	El Khuffash et al, 2014[31]	17/23	74 %
11	Aikio et al, 2014[32]	18/23	78 %
12	Tekgunduz et al, 2014[33]	15/23	65 %
13	Ozdemir et al, 2014[34]	15/23	65 %
14	Terrin et al, 2014[35]	17/23	74 %
15	El Khuffash et al, 2015[36]	19/23	82.5 %
16	Roofthooft et al, 2015[37]	20/23	87 %
17	Weisz et al,2016[38]	19/23	82.5 %
18	Memisoglou et al, 2016[39]	17/23	74 %
19	Valerio et al, 2016[40]	20/23	87 %
20	Luecke et al, 2017[41]	19/23	82.5 %
21	Pharande et al, 2018[42]	20/23	87 %
22	Tofe et al, 2018[43]	13/23	56 %

7 articles had a STROBE compliance score > 75 % (32 %).

13 articles had a STROBE compliance score >60 % (59 %).

15 articles had a STROBE compliance score >50 % (68 %).

7 articles had a STROBE compliance score < 50 % (32 %).

The frequency of reporting of each STROBE checklist item in the 22 articles combined, as an absolute number and as a percentage, is depicted in table 7.

TABLE 7

Section/Topic	Item No	Number of articles reporting the item	Percentage (%)
Title and Abstract			
Study design	1a	13/22	59
Informative summary	1b	18/22	82
Introduction			
Background/Rationale	2	20/22	91
Objectives	3	19/22	86
Methods			
Study design	4	16/22	73
Setting	5	12/22	54.5
Participants	6	22/22	100
Variables	7	16/22	73
Data sources / Measurements	8	13/22	59
Bias	9	1/22	4.5
Study size	10	15/22	68
Quantative variables	11	4/22	18
Statistical methods	12	12/22	54.5
Participants	13	22/22	100
Descriptive data	14	21/22	95.5
Outcome data	15	22/22	100
Main results	16	1/22	4.5
Other analyses	17	7/22	32
Discussion			
Key results	18	22/22	100
Limitations	19	14/22	64
Interpretation	20	18/22	82
Generalisability	21	10/22	45.5
Other information			
Funding	22	10/22	45.5

Only 9 of the 23 STROBE items (35 %) were addressed in 75 % or more of the articles published between 2011 and 2018 : Informative summary (1b), background/rationale (2), objectives (3), participants (6), participants (13), descriptive data (14), outcome data (15), key results (18) and interpretation (20). Bias (9), quantative variables (11), main results (16) and other analyses (17) were the most underreported items.

The articles were published in fourteen different journals. The impact factors of the journals in comparison with the STROBE compliance score of the articles published are reported in table 8.

TABLE 8 : Impact factors of Journals where the articles were published

JOURNAL	ARTICLES	IMPACT FACTOR	STROBE SCORE
PEDIATRICS	1	5.297	43.5
ARCHIVES OF DISEASE OF CHILDHOOD : FETAL AND NEONATAL EDITION	2 15	3.953	35 82.5
PEDIATRIC RESEARCH	10	3.123	74
NEONATOLOGY	3 4	2.688	74 26
FRONTIERS IN PEDIATRICS	22	2.335	56
EUROPEAN JOURNAL OF PEDIATRICS	16 19	2.242	87 87
JOURNAL OF PERINATOLOGY	9 17	2.183	43.5 82.5
ITALIAN JOURNAL OF PEDIATRICS	14	1.776	74
JOURNAL OF MATERNAL	5	1.493	52

FETAL AND NEONATAL MEDICINE	8 11 18		43.5 78 74
JOURNAL OF CLINICAL NEONATOLOGY	6		35
PEDIATRIC CARDIOLOGY	13 21	1.54	65 87
JOURNAL OF POSTGRADUATE MEDICINE	7	1.095	43.5
CARDIOLOGY IN THE YOUNG	12	0.978	65
JOURNAL OF PEDIATRIC PHARMACOLOGY AND THERAPEUTICS	20		82.5

CONCLUSIONS

The use of paracetamol was introduced only recently in the management of the patent ductus arteriosus in preterm infants. The published RCTs and Observational studies concerning its effectiveness and safety compared to those of NSAIDs, used for the last 4 decades in the treatment of PDA, are limited. Their quality, as assessed using the CONSORT statement and the STROBE statement respectively, is rated as moderate. This is in contrast with the fact that they are published years after the publication of the CONSORT and STROBE statements. Essential medical and statistical information is well reported, whereas more sophisticated methodological issues (like bias, blinding, additional analyses) are rarely described. The impact factor of the Journals they are

published in, is low : < 4 for RCTs and < 6 for the Observational studies. Due to the small number of studies, the short period of existing publications and the generally low impact factor of the journals, no differencess between separate groups could be investigated. Yet, there is a trend for improvement in the STROBE adherence over time for the Observational studies.

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