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SYSTEMATIC REVIEW ON THE RELEVANCY OF PARACETAMOL AND BREASTFEEDING POST INFANTS VACCINATION

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Background: Paracetamol may be use as antipyretic agent for the treatment of fever, as well as an analgesic in the treatment of mild to moderate pain on post vaccination in infants. The use of Paracetamol during fever may be or may not be recommended since it may alter natural human body immune response although it may reduce pain.
Objectives: This study described the relevancy of Paracetamol use post infants vaccination based on data collection systematic review analyses. This study aims to describe the effectiveness of breastfeeding in reducing pain and Paracetamol in reducing fever and pain post infants vaccination.
Data Sources and Study Selection: Electronic literature search by hand searching six (6) databases which include Ovid LWW Total Access Collection and Medline, CINAHL (Cumulative Index to Nursing and Alled Health Literature) Plus with Fulltext, Science Direct, Proquest Dissertations and Theses, Proquest Education Journal and Proquest Health and Medical Complete. Additionally, manual reference checks of all articles on Paracetamol and breastfeeding post infants vaccination published in English Language between 1978 and 2017. Two level of screening were used on 9614 citations which include screening of abstracts and titles followed by full text screening.
Data Synthesis: Data synthesis were tabulated into study characteristics, quality and effects. Authors of trials were not contacted for further details or provision of original data if the published report contained insufficient information. The study findings, as reported by the authors, were included in this review. The data in this research cannot be pool due to not enough data regarding odd ratio or relative risk as well as confidence interval in each study.
Results: Systematic review of breastfeeding included three (3) studies from 9614 of database searching. The reviews of all these three (3) studies found significant benefit from breastfed in pain score and duration of crying as well as behavioral changes. None study stated the unbeneficial of breastfeeding before, during and after immunization. Meanwhile, systematic review of Paracetamol effectiveness included four (4) studies from 1177 of database searching. The reviews of two (2) studies found significant benefit from prophylaxis Paracetamol in fever and only one (1) study found significant benefit from prophylaxis Paracetamol in fussiness. On the other hand, there was one (1) study found not signifiant benefit from prophylaxis Paracetamol in fever. Other than that, there were two (2) studies evaluate the safety of prophylactic Paracetamol which revealed different outcomes, in which study by Prymula et. al. in 2009 found that antibody responses to several antigens were reduced significantly, and the other study by Uhari et. al. in 1988 found that antibody titres to DTP bacteria of placebo and PCM not differ significantly. Thus, Paracetamol seems to be not relevant post infants vaccination and breastfeeding was found to be beneficial post infants vaccination.
Conclusions: The relevancy of giving Paracetamol post all types of vaccination may be questionable since the safety issue of this intervention may be arised. Breastfeeding before,

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during and after immunization are recommended for pain reduction as it was proved effectively. Finally, in deciding Paracetamol to be of rational use following infants immunization, it may need for further research which include in depth quantitative and qualitative studies to identify specific problem and causes regarding this issue.
Keywords: Paracetamol, breastfeeding, post, childhood, prophylactic, immunization, vaccination

INTRODUCTION

Paracetamol may be use as antipyretic agent for the treatment of fever, as well as an analgesic in the treatment of mild to moderate pain on post vaccination in child (Drug Information Handbook, 2006). Current recommendations of different guidelines (American Academy of Pediatrics in 2003 and the Advisory Committee on Immunization Practices in 2002 as well as College of Paediatrics, Academy of Medicine of Malaysia in 2001 and the '*Bahagian Pembangunan Kesihatan Keluarga, Kementerian Kesihatan Malaysia*' in 2008) note the option to give Paracetamol prophylaxis for childhood vaccinations, but neither promote nor discourage routine use of prophylaxis. (Jackson, Peterson, Dunn, Hambidge, Dunstan, Starkovich, Yu, Benoit, Dominguez-Islas, Carste, Benson, Nelson, 2011). The theoretical explanation was Paracetamol will inhibit the synthesis of Prostaglandin in the hypothalamus, thus inhibits the hypothalamic heat-regulating center and finally produces antipyeresis; as well as peripherally blocks pain impulse generation, thus producing analgesic effects (Drug Information Handbook, 2006). This explains why the use of Paracetamol during fever may be or may not be recommended since it may alter natural human body immune response although it may reduce pain.

The Medical News by The Lancet on 19thOct 2009 stated that 'Paracetamol, an antipyretic post vaccination is less likely to be counterproductive'. The proof is that antibody Geometric Mean Concentration (GMC) is lower significant in Paracetamol group than in control group (Medical News Today, 2009, Prymula, *et. al,* 2009). In fact, some evidence showed that prophylactic administration of an antipyretic drug around the time of vaccination may lower antibody responses to some vaccines (Immunisation Against Infectious Disease: How Vaccines Work?.*The Green Book*, 2006 and Jason and Philip, 2010). Besides, the vaccine itself may not be effective if Paracetamol is given at early stage to prevent fever following immunization. It may cause fewer antibody produced, thus it is possible that the vaccine may not work well (Immunisation Against Infectious Disease: How Vaccines Work?.*The Green Book*, 2006). Thus, this may warrant the use of Paracetamol post vaccination in infants since it may contradicts the Worlds Health Organization's Expanded Programme on Immunization main aim.

The reduction of fever and pain following infants immunization is a high priority for the international community. Ancient recommendation for fever and pain treatment need to be revised since treating fever at early stage and pain following infants immunization by Paracetamol may be questionable since it may causes the vaccine injected less effective (Prymula, et. al, 2009). Evidence-based health policies and programmes aiming to reduce fever and pain following infants immunization need reliable and valid information. Effective interventions to improve overall infants health need targeted health and social policies that are informed by reliable and valid epidemiological data. The author undertook a systematic review that aimed to estimate the effectiveness of Paracetamol for fever and natural intervention (in which breastfeeding) for pain following infants vaccination. Interventions used in the studies of antipyretic property of Paracetamol were placed in two (2) intervention categories: (i) administration of prophylactic Paracetamol and (ii) administration of Paracetamol during fever. Meanwhile, interventions used in the studies of analgesic property

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of breastfeeding were placed in two (2) categories: (i) breastfeeding (ii) held in mothers' arms but not fed. This study aims to determine the efficacy of breastfeeding as an analgesic properties and the efficacy as well as safety of Paracetamol as an antipyeretic properties post infants vaccination and provide evidence-based recommendations for clinical practice.

METHOD

Search Strategies

A wide range of medical, environmental and scientific databases were search to identify primary studies of the effects of breastfeeding before, during and after immunization as well as the effects of antipyretic agent following infants immunization in order to capture as many relevant citations as possible. The electronic searches were supplemented by hand searching of six (6) databases which accessed through EzProxy for Off Campus Access Online Database for International Islamic University Malaysia (IIUM) Students and Staffs in which via https://login .ezlib.iium.edu.my/login. The databases include Ovid LWW Total Access Collection and Medline, CINAHL (Cumulative Index to Nursing and Alled Health Literature) Plus with Fulltext, Science Direct, Proquest Dissertations and Theses, Proquest Education Journal and Proquest Health and Medical Complete. Additionally, manual reference checks of all articles on Paracetamol and breastfeeding post childhood vaccination published in English Language between 1978 and 2017. Two level of screening were used on 9614 citations. The keywords that were used include:

Database searches	**Items Measure**	**Keywords**
Ovid LWW Total Access Collection and Medline, CINAHL Plus with Fulltext, Science Direct, Proquest Dissertations and Theses, Proquest Education Journal and Proquest Health and Medical Complete (data collected from published paper from 1987 until 2017)	1) Pain 2) Breastfeeding	'breastfeeding; pain or analgesia; following or post; immunization or vaccination; infant or newborn'
	3) Fever and pain 4) Paracetamol	'feverish or febrile or fever; breastfeeding; temperature decrease; antipyretic; analgesic; following or post; immunization or vaccination; infant or newborn; antibody'

Table 1: Keywords for Systematic Review

The titles and abstracts of the articles were scanned by two (2) reviewers (N. S. and S. H. S.). Articles selected by the reviewers were retrieved in full and assessed for eligibility by the two (2) reviewers. The reviewers did not contact the authors to identify additional studies

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but the reviewers referred to reference lists from the identified trials. The reviewers were not blinded to the authors or settings of the scanned articles.

Study Selection: Inclusion Criteria

Only reports with information on infants (for this study defined as up to 1 year of age) were included. All randomized trials and cohort (nonrandomized) studies that included a placebo or unexposed group were included for the determination of efficacy. Trials of different designs, however, were handled separately. The efficacy of breastfeeding as an analgesia and physical intervention of fever as antipyretic were reviewed for the immunization and/ vaccination procedure only. All prospective studies that reported data on variables of noxious stimuli with behavioral, physiologic, hormonal, and metabolic changes were included since infants respond to these variables. For determination of safety, all prospective studies were included. Paper that have funding sources also included in this study.

Study Selection: Exclusion Criteria

Reviews, meta-analyses, editorials, commentary or conference abstracts were excluded in this study. Meta-analysis was excluded in this study because it was not feasible due to extensive variation in study features and methodological quality (Coomarasamy A., Taylor R. & Khan K. S., 2003)

Data Collection and Analysis

There were two reviewers in this study. The study from World Health Organization also included two reviewers for systematic review (Khan K. S., Wojdyla D., Say L., Gülmezoglu A. M., Look P. F. A. V., 2006). The first reviewer screened all titles and abstracts of papers identified by the literature search. The second reviewer handled duplicate screening on a random selection of found titles or abstracts. The disagreements were discusses between both reviewers. All studied that had been identified as potentially relevant were retrieved and read in full to determine eligibility for inclusion.

Data extractions were conducted by using a pre-defined data extraction template. Data that were extracted include design characteristics, study population and country, sample size, sample selection, age of participants, the exposure and outcome measures and results.

Primary Outcome

The primary outcome was pain and/ fever following infants immunization. Examples of validated observational measures for pain were a Douleur Aigue du Nouveau-ne (DAN) Scale, Facial Pain Rating Scale and Neonatal / Infant Pain Scale (NIPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and cry duration. Examples of observational measures for fever were babies' fussiness and temperature reading more than and at 38°C.

Validity Assessment

The included trials were not masked to the reviewers (N.S. and S.H.S.). The methodological quality of each study was assessed by two (2) independent reviewers using the Crowe Critical Appraisal Tool (CCAT) (Donnelly, Hickey, Burns, Murphy, Doyle, 2015) to investigate internal validity (the extent to which the information is probably free of bias) with the following attributes. The CCAT was developed based on a wide number of previous critical appraisal tools, general research methods theory and reporting guidelines (Donnelley et. al., 2015). The tool was validated and undergone testing for reliability and validity (Donnelly et. al., 2015). The CCAT appraised papers included in the review in eight (8) categories. This tool uses scoring system in which each category is scored from zero (0) in which no evidence

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to five (5) in which highest evidence. Total scores of each study are presented as a percentage. The average scores of reviewers were reported.

Data Abstraction

Data from each eligible study were extracted individually on custom-made data-collection forms (designed specifically for each intervention) by two (2) reviewers (N.S. or S.H.S.), and the results were compared. The reviewers resolved any disagreements through discussion.

Study Characteristics

Characteristics of included studies as well as the country of being conducted were displayed in Table 2 (for effectiveness of breastfeeding) and 3 (for effectiveness of prophylactic Paracetamol and its safety). This study included research published in 1987 onwards.

Data Synthesis

Data syntheses were tabulated into study characteristics, quality and effects. The original review of summarizing the evidence from studies of variable design will provide details how the differences between study results were investigated and how they were summarized (Khan, 2003).

Authors of trials were not contacted for further details or provision of original data if the published report contained insufficient information. The study findings, as reported by the authors, were included in this review.

The data in this research cannot be pool due to not enough data regarding odd ratio or relative risk as well as confidence interval in each study.

Secondary Outcomes

Local and adverse reactions following infants immunization was reviewed in the study of prophylactic Pracetamol post infants vaccination.

RESULTS

Effectiveness of breastfeeding as an analgesic property for pain following childhood vaccination

Study Descriptions

Figure 1 presents a flow diagramme of the search strategy. After duplicates are removed the search retrieved 9504, of which 9481 are excluded (9400 on review of abstracts / title and a further 81 after full text papers assessment). 23 of reviewed full text articles and 19 were excluded because outcome and exposure not measured. Among these, one (1) was excluded because the age was not within inclusion criteria. Finally, data from three (3) journal articles included in the systematic review.

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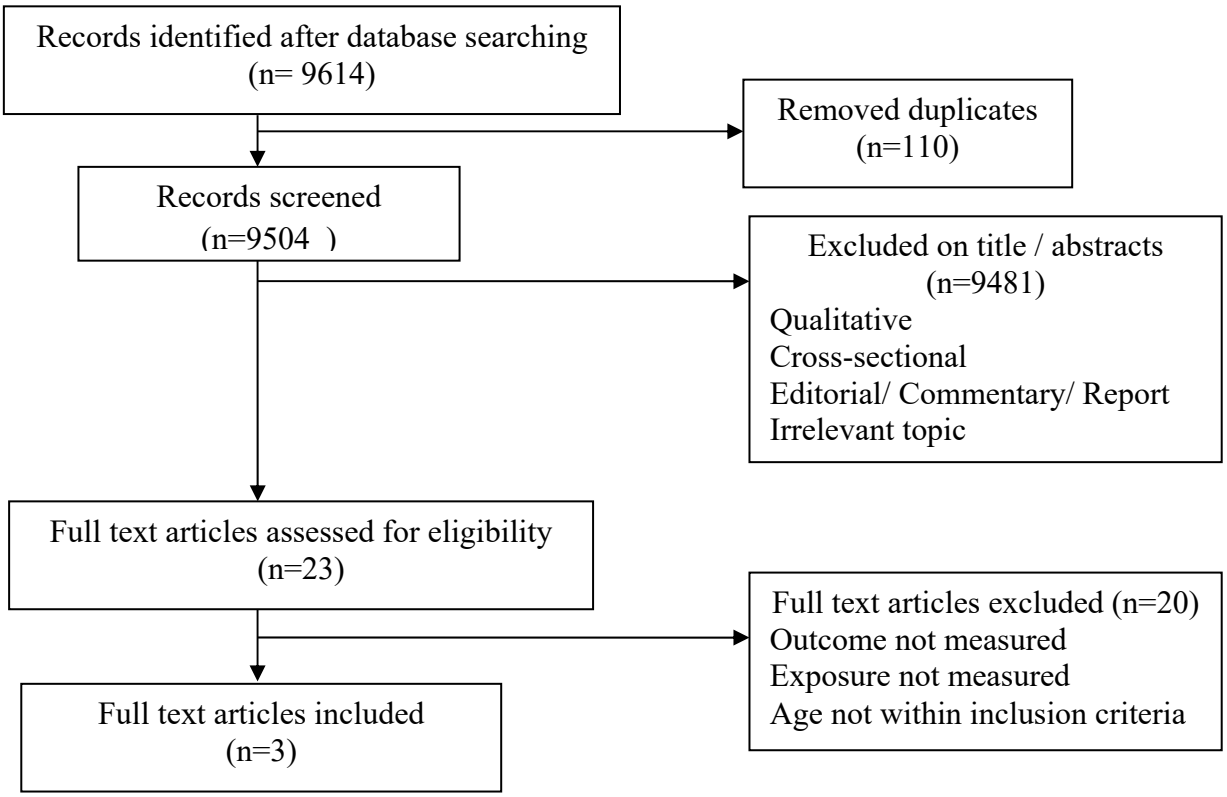
Figure 1: Flow diagramme of research strategy for effectiveness of breastfeeding as pain intervention post childhood vaccination



Study Characteristics

Overall, there were three (3) studies that met the inclusion criteria and eligible for study of the effectiveness of breastfeeding as an analgesic property for pain following immunization in infants. These researches were conducted mainly in East Coast country region which include one (1) in Iran, one (1) in Jordan and one (1) in Turkey. Studies began in 2007 and the latest study was in 2013.

These studies addressed two (2) of the intervention categories identified in the protocol: (i) breastfeeding or (ii) held in mothers' arms but not fed. All studies included age of babies not more than one (1) year.

The researcher included randomized control trial and quasi controlled trial that compared breastfeeding and combined interventions of interest with a placebo or control group for pain management during immunization in children aged from 0months to 1 year of age. Among these, there were two (2) studies that were randomized controlled trial and only one (1) study that was quasi controlled trial. The primary outcome measure for pain was made by health care worker or observer using observational methods; for example Douleur Aigue du Nouveau-ne (DAN) Scale, Facial Pain Rating Scale and Neonatal / Infant Pain Scale (NIPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and cry duration. However, all of these studies did not mentioned the duration of breastfeeding.

Among these three (3) studies, one (1) did not contain information about receiving approval by institutional review board or ethics committee. On the other hand, two (2) of three (3) studies mentioned that they obtained approval from institutional ethics review board

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or committee. All of these studies mentioned that they obtained information consent from the mothers.

Methodologic quality of the included studies

The percentage of agreement on all key items for assessment of the methodologic quality of the three (3) studies was from 75% till 83%; disagreements were resolved by consensus. Three (3) trials which include 316 infants aged zero (0) to 12 months examined the analgesic effects of breastfeeding.

Effects of breastfeeding post infants vaccination

In all three (3) studies, infants who were breastfeed before, during and after procedure were compared with infants who were not breastfed. The level of pain was measured using cry duration (Razek et. al., 2009 and Efe et. al., 2007), Neonatal Infant Pain Scale (NIPS) (Razek et. al., 2009), Douleur Aigue du Nouveau-ne (DAN) Scale (Modarres et. al, 2013), Facial Pain Rating Scale (FPS) (Razek at. al., 2009), Children's Hospital of Eastern Ontarion Pain Scale (CHEOPS) as well as behavioral changes (Efe et. al., 2007).

The reviews of all studies found significant benefit from breastfed in pain score and duration of crying as well as behavioral changes. Pain score of study by one (1) study revealed that significant lower pain score in which $p<0.001$ in study by Razek et. al., 2009 for experimental group (breastfeeding group) than control group (not breastfed). One study by Razek et. al. in 2009 noted that FPS for intervention group represents little more pain (38%) than control group which represents hurt even more Score 3 that indicate pain. Two (2) studies evaluated crying time and it was revealed that crying time was shorter in intervention group rather than control group (Razek et. al., 2009, Efe et. al., 2007). Other than that, among two (2) studies that evaluated behavioral changes in which heart rate and oxygen saturation, one (1) of them was found that statistically significant difference before and after immunization between intervention and control group ($p< 0.005$). The other one (1) study found that heart rate and oxygen saturation level almost same in both groups.

Breastfeeding had also been studied as an alternative to painful procedure during immunization recently, with positive outcomes. Studies had demonstrated that breastfeeding (Modarres et. al, 2013, Razek et. al., 2009 and Efe et. al., 2007), maternal holding (Efe et. al., 2007) and skin to skin contact (Razek et. al., 2009 and Efe,. et. al., 2007) statistically significantly reduced pain (Modarres et. al., 2013) and crying duration (Razek et. al., 2009 and Efe et. al., 2007) in children following immunization.

These studies showed that breastfeeding is effective as pain relief following immunization in infants

Effectiveness of prophylactic Paracteamol as an antipyretic and analgesic properties as well as its safety for fever following childhood immunization

Study Descriptions

Figure 2 presents a flow diagram of the search strategy. After duplicates were removed the search retrieved 1176, of which 1165 were excluded (1100 on review of abstracts / title and a further 65 after full text assessment). 11 of reviewed full text articles and two (2) were excluded because outcome and exposure not measured. Among these, five (5) were excluded because the age were not within inclusion criteria. Finally, data from four (4) journal articles were included in the systematic review.

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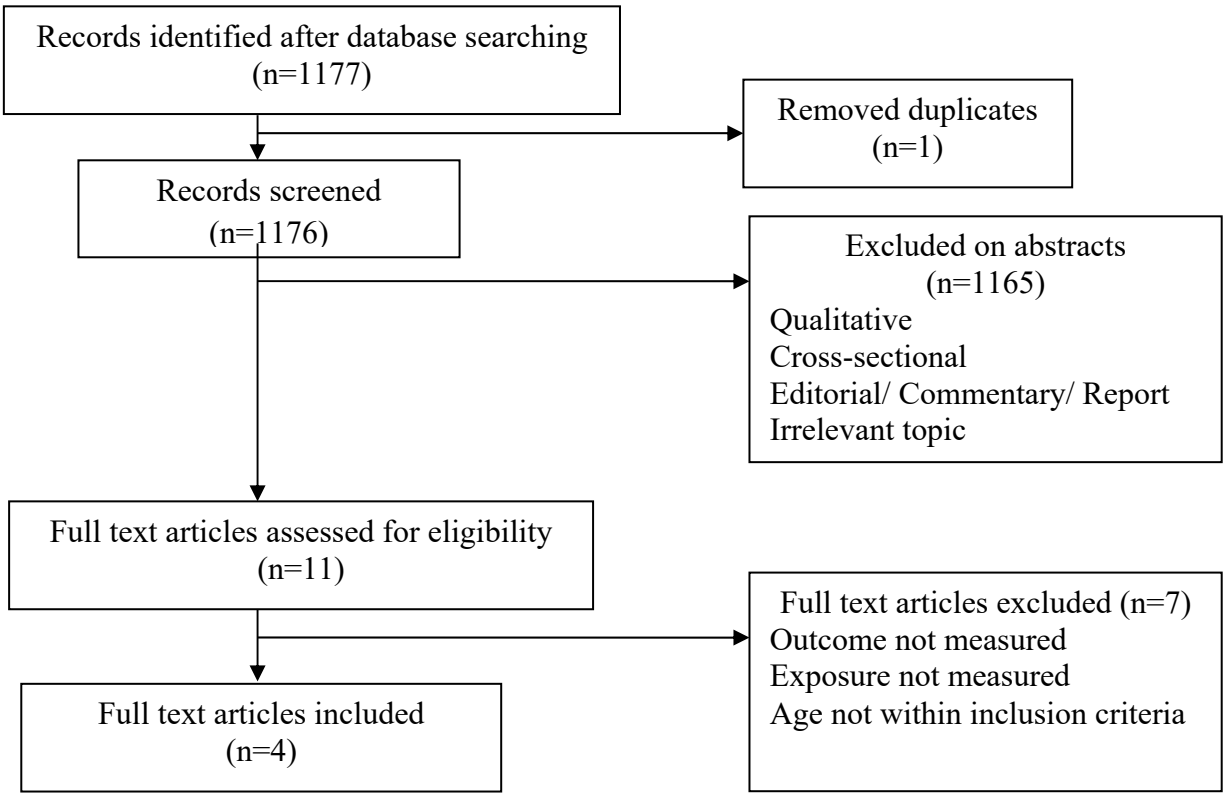
Figure 2: Flow diagramme of research strategy for effectiveness of prophylactic Paracetamol as fever reduction post childhood vaccination



Study Characteristics

Overall, there were four (4) studies were assessed as being of sufficient quality to be included in the review. These researches were conducted mainly in Europe and East Coast country region which include one (1) in Czech Republic, one (1) in United States of America (USA), one (1) in Germany and one (1) in Finland. Studies began in 1988 and the latest study was in 2013.

As mentioned before, these studies addressed two (2) intervention categories: (i) administration of prophylactic Paracetamol and (ii) non-prophylactic Paracetamol for fever following childhood immunization.

All of these studies evaluated either the child was having fever or not (Rose et. al, 2013, Jackson et. al, 2011, Prymula et. al., 2009 and Uhari et. al., 1988), only one (1) study evaluated local systemic reactions (Rose at. al., 2013), two (2) studies evaluated adverse reactions (Rose et. al., 2013 and Uhari et. al., 1988) and only one (1) study evaluated baby condition (Jackson et. al., 2011) as well as only two (2) studies evaluated antibody of children (Prymula et. al., 2009 and Uhari et. al., 1988). All studies included age of babies from about six (6) weeks to around one (1) year of age (Rose et. al, 2013, Jackson et. al., 2011, Prymula et. al., 2009 and Uhari et. al., 1988). All of these studies also included in the systematic review.

The researcher included all randomised controlled trial that compared prophylactic Paracetamol use and/ no prophylactic Paracetamol use post infants vaccination. The primary outcome measure for fever was made by parents completed the diary and/ questionnaires given by the researcher of the study,

Among these four (4) studies, three (3) of them mentioned that they obtained approval from institutional ethics review board or committee (Rose et al., 2013, Jackson et. al, 2011 and Prymula et. al., 2009). All of these studies mentioned that they obtained information consent from parents and/ legal guardian except the study by Uhari et. al (1988) did not mentioned they obtained consent from guardians, however they had obtained Ethical Approval from Medical Faculty of Oulu University.

Methodologic quality of the included studies

The percentage of agreement on all key items for assessment of the methodologic quality of the four (4) studies were ranging from 65% till 88%; disagreements were resolved by consensus. Four (4) trials which include 1156 infants aged zero (0) to 12 months of age examined the antipyretic effect of Paracetamol.

Effect of prophylactic PCM for fever and pain following childhood immunization

All studies compared children receiving prophylactic or non-prophylactic PCM post vaccination. Fever was measured using body temperature ≥38C or >39.5C of axillary or rectal temperature, meanwhile baby condition was measured by the appearance of fussiness.

The reviews of two (2) studies found significant benefit from prophylaxis Paracetamol in fever (Rose et. al., 2013 and Prymula et. al., 2009) and only one (1) study found significant benefit from prophylaxis Paracetamol in fussiness (Jackson et. al., 2011). On the other hand, there was one (1) study found not signifiant benefit from prophylaxis Paracetamol in fever (Uhari et. al., 1988).

Local and adverse reactions following immunization

Other than that, recent one (1) study found that local systemic reactions were less frequent in prophylaxis group, but no significant difference between groups (Rose et. al., 2013). In contrast, there was none study showed that there was significant reductions in local systemic reactions of prophylactic group (Jackson et. al, 2011, Prymula et. al., 2009 and Uhari et. al., 1988).

Besides, there was one (1) study stated that no vaccine-related serious adverse event reported (Rose et. al., 2013), and there was none study mentioned that prophylactic PCM can significantly reduced frequency and severity of common adverse reactions (Rose et. al, 2013, Jackson et. al, 2011, Prymula et. al., 2009 and Uhari et. al., 1988). The study by Uhari et. al. in 1988 revealed that no significant difference in occurrence of minor adverse events.

Safety of prophylactic Paracetamol post infants vaccination

Other than that, there were two (2) studies evaluate the safety of prophylactic Paracetamol (Prymula et. al., 2009 and Uhari et. al., 1988). These studies revealed different outcomes, in which study by Prymula et. al. in 2009 found that antibody responses to several antigens were reduced significantly, and the other study by Uhari et. al. in 1988 found that antibody titres to DTP bacteria of placebo and PCM not differ significantly. The study by Prymula et. al. in 2009 also noted that prophylactic Paracetamol at time of vaccination should not routinely recommended although febrile reactions significantly reduced since antibody responses to several antigens were reduced significantly.

Prophylactic Paracetamol had been studied to have beneficial effects as antipyretic property post vaccination in children. However this outcome is questionable since there were also studies that rejected the benefit of prophylactic Paracetamol. Other than that, there was one (1) study found that prophylactic Paracetamol may significantly reduced the antibody of infants (Prymula et. al., 2009). Additionally there was one (1) study by Jackson et. al. in 2011

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was stopped because the result of study by Prymula et. al. in 2009. The study by Jackson et. al. in 2011 also noted that the potential benefit of Paracetamol prophylaxis in reducing the risk of fever and associated adverse events following contemporary infants immunizations appear to be outweighted by the potential harmful effects of Paracetamol prophylaxis on vaccine immune responses.

DISCUSSION

Paracetamol was use as an antipyeretic agent and analgesic post vaccination in infants. However, its use seems questionable since in theory the use of Paracetamol at early stage of fever may alter the vaccine function and causes vaccine less effective (Prymula, *et. al,* 2009). Theoretically, the use of Paracetamol may interferes natural body immune response by inhibiting Prostaglandins (PGs) which involve in natural human body defense mechanisms. Meanwhile, most vaccines injected to the child are originated from the live attenuated organism itself (organism that may cause infection) in which they work by replicating of the live organisms over days or weeks thus covering the immunity.

Prophylactic antipyretic of Paracetamol significantly reduced the febrile reactions of ≥38ºC after vaccinations. There were statistically significant differences in antibody responses between two groups in which lower in prophylactic Paracetamol group. Recent one (1) study showed that there were significant reductions in the local and systemic symptoms in prophylaxis group, but no significant difference between groups (Rose et. al., 2013).

Only two (2) trials studied the antibody response (Prymula et. al, 2009 and Uhari, et. al. 1988), thus the data cannot be pooled. Studies used different doses/ schedules antipyretic administration as well as age of participants or timing of administration also markedly differed among studies.

There were none of studies that were identified in the literature search evaluated the effectiveness of oral analgesic in which Paracteamol for immunization pain (Shah, Taddio, Rieder, 2009). Pediatricians may recommend oral analgesics to parents as a pain-relieving intervention for vaccine injection pain (Shah et. al., 2009). However, no evidence was found to recommend the use of either agent as a method of pain relief for vaccine injections. There was no study of Paractemol effects on vaccine injection pain was identified, however this agent was widely used. Thus, a study that addresses this issue may be warranted.

This study found that breastfeeding before, during and after immunization reduced pain, as assessed using cry duration, DAN scale, FPS, NIPS, CHEOPS and or behavioral changes (heart rate and oxygen saturation. The proposed mechanisms of breastfeeding provides analgesia include (i) breastfeeding, (ii) maternal holding and skin to skin contact (Efe et. al., 2007).

The findings of systemic review were consistent with the effectiveness of breastfeeding as an analgesic property in reducing pain of injection immunization in neonates (Shah et. al., 2009). Breastfeeding is a natural, cost-neutral, time-efficient, and convenient intervention that could be easily adopted from the perspectives of health care providers and parents (Shah et. al., 2009). Other than nutritional and psychological value of breastfeeding, the analgesic properties may encourage more mothers to breastfeed (Shah et. al., 2009).

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LIMITATION

Methodologic challenges and limitations of this review include the small number of studies for breastfeeding interventions, small sample size, limited age range of participants, limited number of vaccines evaluated and variability in pain assessments. The included trials used various methods of assessing pain in infants, which made it difficult to combine and contrast the results.

RECOMMENDATION FOR FUTURE RESEARCH

Finally, in deciding Paracetamol to be rational use following infants immunization, it may need for further research which include in depth quantitative and qualitative studies to identify specific problem and causes regarding this issue.

Based on the researcher's review, areas for future research were identified. The role of expressed breast milk has not been studies, and further research is needed. Finally, studies addressing whether the gap between research findings and clinical practice can be narrowed by communication and dissemination strategies aimed at practitioners, professional groups, and families will be important in establishing the common goal of pain-free, tolerable, and effective immunization for infants.

Future trials should focus on the timing (before, with or after) and route (oral or rectal) of administration of Paracetamol as well as on the subgroup of infants (term or preterm) for any correlation with the immune response. Future trials should focus on trial examining the prophylactic effect of Paracetamol post vaccination antibody response since there was lack of studies regarding this issue. The mechanism underlying the reduction in immune / antibody response should also be explored. Trials should also be conducted in developing countries where over-the-counter use of antipyretics (including prophylactic) are common. Other cofounding factors that might affect the antibody response such as infants sleep post-immunization should also be studied.

CONCLUSION

In identifying the problem in drug use, this preliminary research need to be conducted as guided by World Health Organization in deciding the relevancy of the supply of Paracetamol post all types of infants immunization.

The relevancy of giving Paracetamol post all types of vaccination may be questionable since the the safety issue of this intervention may be arised.

Although prophylactic antipyretic Paracetamol administration leads to relief of local and systemic symptoms after vaccinations, there was a reduction in antibody responses to some vaccine antigens. Future trials and surveillance programs should also aim at assessing the effectiveness of programs where prophylactic Paracetamol is given. The timing of administration of Paracetamol should be discusses with the parents after explaining the benefits and risks.

Breastfeeding before, during and after immunization are recommended for pain reduction as systematic review of this study showed its proven effectiveness.

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APPENDIX I

Table 2: Summary of Relevant Research on Effectiveness of Breastfeeding Used as an Intervention to Decrease Pain in Infants

No.	Author; country; year of publication	Research design	Study population; care recipient % boys; care recipient age mean (SD)	Sample size: baseline; follow-up	Exposure measure	Outcome measure	Quality score (%)	Statistical results	Conclusion
1	Modarres, Jazayeri, Rahnama, Montazeri, Iran, 2013 [Funding Source: Instituitional Review Board of the Tehran University of Medical Sciences]	True experiment: Placebo controlled trial	Full term neonates breastfed 2 minutes before, during and after Hepatitis B immunization or held in mothers' arms but not fed; 83% boys; 39.4 (1.2) in control group and 39.1 (1.3) in experimental group weeks	130; 130; 130	1) Pain score measured using DAN scale (Facial expressions, limb movements and vocal expression)	Pain score	75	1) Significant difference in mean of facial expressions of neonates between the control 2.58 (SD=0.72) and experimental groups 1.39 (SD=0.65). ($p<0.001$). 2) Significant differences between two groups in mean of limb movements 1.92 (SD=0.69) and experimental groups 0.83 (SD=0.51). ($p<0.001$) 3) Significant differences in mean of vocal expression between control 2.28 (SD=0.57) and experimental groups 1.31 (SD=0.68). ($p<0.001$). 4) Significant difference in mean of Total DAN scores between control 6.78 (SD=1.69) and experimental groups 3.52 (SD=1.37). ($p<0.001$)	Breastfeeding reduces pain and is effective way for pain relief during Hepatitis B injection

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2.	Razek, El-Dein, Jordan, 2009 [Funding Source: None]	Quasi experiment: Counter balanced (cross-over)	Infants either breastfed or not; 64.2% boys; 1 to 12 months of age	120; 120; 120	1) Pain score measured using Facial Pain Rating Scale before, during and after procedure 2) Duration of crying 3) Heart rates	1) Pain rating scale 2) Crying time 3) Heart rate	75	1) Significant difference in Facial Pain Rating Scale between control and experimental group ($p<0.05$) 2) Significant difference in mean of Duration of Crying between control 148.66sec (SD13.96) and experimental groups 125.33sec (SD12.18). ($p<0.005$) 3) Not differ significantly in mean of heart rate elevation between control group (before procedure 125.22bpm SD 29.15, after procedure 162.25bpm SD 40.22) and experimental group (before procedure 128.59bpm SD 15.45, after procedure 149.210bpm SD 20.510). p before procedure = 1.330, p after procedure=none	Breastfeeding and skin to skin contact significantly reduced the pain in infants receiving immunization. Pain Score also showed lesser in breastfeeding group.
3.	Efe, Ozer, Turkey, 2007 [Funding Source: Akdeniz University Scientific Research Project Unit]	True experiment: Placebo controlled trial	Healthy infants receiving 2^{nd}, 3^{rd} or 4^{th} immunization of IM DTP***** either breastfed before, during and after injection or given not breastfed; 56.1% boys; 3.08 ± 1.32 months control, 2.79 ± 1.13 months breastfed	66; 66; 66	1) Length of crying 2) Heart rate 3) Oxygen saturation levels	1) Crying time 2) Behavioural changes	83	1) Significant difference in mean of Crying duration between control 76.24sec (SD49.61) and experimental 35.85sec (SD40.11). $p=0.001$ 2) Not differ significantly in mean of heart rate elevation between control group (during procedure 129.58bpm SD 38.32, after procedure146.36bpm SD	Breastfeeding, maternal holding, and skin to skin contact significantly reduced crying time in infants receiving immunization injection for DTP

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								31.06) and experimental group (during procedure 138.85bpm SD 35.89, after procedure153.36bpm SD 29.60). p during procedure = 0.31, p after procedure=0.352 3) Not differ significantly in mean of oxygen saturation between control group (during procedure 95.85% SD 4.18, after procedure 95.33% SD 4.17) and experimental group (during procedure 96.64% SD 2.93, after procedure 95.97% SD 3.08). p during procedure = 0.379, p after procedure=0.483	

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Table 3: Summary of Relevant Research on Effectiveness of Prophylactic Antipyretic Used as an Intervention to Decrease Fever in Infants and its Safety Issue

No.	Author; country; year of publication	Research design	Study population; care recipient % boys; care recipient age mean (SD)	Sample size: baseline; follow-up	Exposure measure	Outcome measure	Quality score	Statistical results	Conclusion
1.	Rose, Juergens, Schmoele-Thoma, Gruber, Baker; Germany; 2013 [Funding Source: Pfizer Inc.]	True experiment: Placebo controlled trial	Healthy infants who received 3 dose infant series of PCV-7 and DTPa-HBV-IPV/Hib plus a toddler dose either received prophylactic Paracetamol at vaccination and at 6to9hour interval thereafter or a control group that received no Paracetamol; 51.5% boys; 2.4 to 11.7months	301; 286; 245	1) Incidence of fever 2) Baby Conditions 3) Crying	1) Fever 2) Drowsiness 3) Decreased appetite 4) Decreased activity 5) Persistent inconsolable crying	83	1) Significant difference in temperature ≥38°C to ≤39°C of control 35.8% and experimental 9.3% groups: → after dose 1 (p<0.001) 2) Significant difference in temperature ≥38°C to ≤39°C of control 43.7% and experimental 19.7% groups: → after dose 2 (p=0.000) 3) Significant difference in temperature ≥38°C to ≤39°C of control 45.6% and experimental 19.3% groups: → after dose 3 (p=0.000) 4) Not significant difference in temperature ≥38°C to ≤39°C of control 60% and experimental 51.5% groups: → after toddler dose (p=0.221)	1) PCM reduced incidence of fever ≥38C, reduction significant in infants but not in toddler 2) Fever > 39C was rare during infant series, thus too few cases for assessment 3) PCM reduced incidence of drowsiness, reduction significant in infants after dose 1 but not in dose 2 and 3 also in toddler 4) PCM reduced incidence of

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								5) Not significant difference in temperature ≥39°C to ≤40°C of control 4% and experimental 0% groups: → after dose 1 (p=0.061) 6) Not significant difference in temperature ≥39°C to ≤40°C of control 1.8% and experimental 0% groups: → after dose 2 (p=0.238) 7) Not significant difference in temperature ≥39°C to ≤40°C of control 1.9% and experimental 1.0% groups: → after dose 3 (p>0.99) 8) Not significant difference in temperature ≥39°C to ≤40°C of control 13.1% and experimental 4.6% groups: → after toddler dose (p=0.072) 9) Not significant difference in temperature >40°C of control 1.1% and experimental 0% groups: → after toddler dose (p>0.99)	decreased appetite, reduction significant in infants after dose 2 but not after dose 1 and 3 also in toddler 5) PCM reduced incidence of decreased activity, reduction significant in infants after dose 2, 3 and in toddler but not after dose 1 6) PCM reduced incidence of persistent inconsolable crying, reduction significant in infants after dose 1 but not in dose 2 and 3 also in toddler

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								10) Significant difference in drowsiness of control 64.7% and experimental 50.4% groups: → after dose 1 (p=0.019) 11) Not significant difference in drowsiness of control 58.3% and experimental 46.5% groups: → after dose 2 (p=0.078) 12) Not significant difference in drowsiness of control 45.6% and experimental 36.4% groups: → after dose 3 (p=0.182) 13) Not significant difference in drowsiness of control 50.4% and experimental 43.5% groups: → after toddler dose (p=0.350) 14) Not significant difference in decreased appetite of control 40% and experimental 30.3% groups: → after dose 1 (p=0.118) 15) Significant difference in decreased appetite of control 42.7% and experimental 26.6% groups: → after dose 2 (p=0.011)	

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								16) Not significant difference in decreased appetite of control 33.6% and experimental 23.0% groups: → after dose 3 (p=0.101) 17) Not significant difference in decreased appetite of control 45.2% and experimental 38.2% groups: → after toddler dose (p=0.336) 18) Not significant difference in decreased activity of control 46.3% and experimental 41.6% groups: → after dose 1 (p=0.457) 19) Significant difference in decreased activity of control 48% and experimental 31% groups: → after dose 2 (p=0.007) 20) Significant difference in decreased activity of control 40% and experimental 23.3% groups: → after dose 3 (p=0.007) 21) Significant difference in decreased activity of control 48.3% and experimental 23.3% groups: → after toddler dose (p=0.005)	

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								22) Significant difference in persistent inconsolable crying of control 20% and experimental 9.5% groups: → after dose 1 (p=0.031) 23) Not significant difference in persistent inconsolable crying of control 15.8% and experimental 9.3% groups: → after dose 2 (p=0.171) 24) Not significant difference in persistent inconsolable crying of control 15.3% and experimental 14% groups: → after dose 3 (p=0.849) 25) Not significant difference in persistent inconsolable crying of control 17.1% and experimental 7.8% groups: → after toddler dose (p=0.056)	

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2.	Jackson, Peterson, Dunn, Hambidge, Dunstan, Starkovich, Yu, Benoit, Dominguez-Islas, Carste, Benson, Nelson; Czech Republic; 2011 [Funding Source: Centre for Disease Control and Preventive (CDC) through America's Health Insurance Plans]	True experiment: Placebo controlled trial	Children received up to 5PCM doses (10-15mg/kg) or placebo following routine vaccinations; 51% boys; 31 weeks to 69 weeks	374; 352; 234	1) Rectal temperature 2) Baby condition	1) Fever 2) Fussiness (more than much more than usual and much more than usual)	83	1) Not significant difference in rectal temperature ≥38°C between the control 22% and experimental groups 14% (p=0.053) 2) Not significant difference in rectal temperature ≥39°C between the control 2% and experimental groups 0% (p=0.08) 3) Significant difference in fussiness (more than much more than usual) between the control 62% and experimental groups 58% (p=0.045) 4) Significant difference in fussiness (much more than usual) between the control 24% and experimental groups 10% (p=0.001)	Acetaminophen may reduce risk of post-vaccination fussiness but not reduce fever

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3.	Prymula, Siegrist, Chlibek, Zemlickova, Vackova, Smetana, Lommel, Kaliskova, Borys, Schuerman; Czech Republic; 2009 [Funding Source: GSK Biologicals]	True experiment: Placebo controlled trial	Children received 3 prophylactic PCM doses every 6 to 8hourly in first 24 hours, or no prophylactic PCM after each vaccination with PHiD-CV co-administered with DTPa-HBV-IPV/Hib and oral human rotavirus vaccines; 51% boys; mean aged at time of 1st dose was 12.3 weeks (SD 2.13).	459; 459; 414	1) Rectal temperature >39.5C after primary and after booster 2) Percentage of child with temperature ≥38C after at least 1 dose of prophylactic PCM after primary and after booster 3) Antibody GMC*** after primary and after boosting	1) Fever 2) Antibody GMC***	88	1) Rectal temperature >39.5C was uncommon in both groups → after primary: 1/226 participants (<1%) in prophylactic PCM group vs 3/233 (1%) in no prophylactic group → after booster: 3/178 (2%) vs 2/172 (1%) 2) Percentage of child with temperature ≥38C after at least 1 dose of prophylactic PCM was significantly lower → after primary: 154/233 (66%) and → after booster: 64/178 (36%) in prophylactic PCM group than in no prophylactic PCM group → after primary: 154/233 (66%) → after booster: 100/172 (58%) 3) Antibody GMC*** were significantly lower in prophylactic PCM group than in no prophylactic PCM group after primary vaccination for all ten pneumococcal vaccine serotypes, protein D, antipolyribosyl-ribitol phosphate, antidiphteria, antitetanus, and antipertactin.	Prophylactic administration of antipyretic drugs at time of vaccination should not routinely recommended although febrile reactions significantly decreased since antibody responses to several antigens were reduced significantly

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4.	Uhari, Hietala, Viljanen; Finland; 1988 [Funding Source: None]	True experiment: Placebo controlled trial	Healthy infants vaccinated with DTP or DTP-inactivated polio vaccine receive placebo or 75mg PCM 4 hours after vaccination; not mentioned; 5months	295; 263; 263	1) Temperature in the evening and the next morning 3) Percentages of temperature with no fever and fever in the evening and the next morning 4) Levels of IgG antibodies (for Diphteria toxoid, Tetanus toxoid, Pertusis bacteria) 4) Frequency of fever during 24hour after DTP vaccination	1) Fever 2) Antibody titres	65	1) Not significant difference in mean of temperature in the evening between the control 37.6°C (SD0.49) and experimental groups 37.6°C (0.65). 95% confidence limits of the difference -0.1-0.1 2) Not significant difference in mean of temperature in the next morning between the control 37.6°C (SD0.53) and experimental groups 37.6°C (0.53). 95% confidence limits of the difference -0.1-0.1 3) Not significant difference in mean percentages of temperature with no fever in the evening between the control 36.5% and experimental groups 37% 4) Not significant difference in mean percentages of temperature with fever in the evening between the control 6.75% and experimental groups 6.75% 5) Not significant difference in mean percentages of	Acetaminophen in a single dose schedule is ineffective in decreasing post-vaccination fever and antibody response also showed not significant differ in control and experimental group

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								temperature with no fever in the next morning between the control 40% and experimental groups 35% 6) Not significant difference in mean percentages of temperature with fever in the next morning between the control 5% and experimental groups 7.25% 7) Not significant difference in mean levels of IgG antibodies (for Diphteria toxoid) between the control 10.5 (SD=6.3) and experimental groups 10.7 (SD=6.6), 95% Confidence limits of differences -3.6-3.2 8) Not significant difference in mean levels of IgG antibodies (for Tetanus toxoid) between the control 16.6 (SD=7.9) and experimental groups 14.2 (SD=8.4), 95% Confidence limits of differences -1.9-6.7 9) Not significant difference in mean levels of IgG antibodies (for Pertusis bacteria) between the control 31.1	

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								(SD=20.0) and experimental groups 34.2 (SD=25.3), 95% Confidence limits of differences -15.0-8.76 10) Not significant difference in frequency of fever during 24 hour period after DTP vaccination between the control 48.5% and experimental groups 44.4%, 95% Confidence limits of differences -8.0-16.	

NS= Not significant
DTP=Diphteria, Tetanus and Pertusis