

## REVIEW ARTICLE

# Historical roots of pain management in infants: A bibliometric analysis using reference publication year spectroscopy

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## Abstract

Retrospective evaluations of the historical role of previously published research are often fraught with subjective bias and misrepresentation, which leads to contested scientific claims. This paper investigates the historical roots of infant pain management using novel quantitative methods to identify the published literature and evaluate its relative importance. A bibliometric analysis named “reference publication year spectroscopy” (RPYS), was performed using the program CitedReferencesExplorer (CRExplorer) to avoid the subjectivity associated with comparative evaluations of individual research studies. Web of Science (WoS) search queries on infant-related synonyms, pain-related synonyms, and analgesia or anesthesia-related synonyms were combined using the Boolean operator “AND,” to identify all publications related to pain management in infants. The RPYS analyses were based on 8697 papers in our publication set containing the citations for 86,268 references. Selected cited publications were associated with peak citation years in 1951, 1954, 1957, 1965, 1987, 1990, 1997, 1999, and 2000. Subsequent analyses suggested that research on infant pain management made rapid progress during 1982–1992. Landmark publications were defined as those belonging to the top 10% of the most frequently referenced publications for longer than 25 years. Through this analysis, we identified and ranked 24 landmark publications to illustrate the historical background and early research on infant pain management. From the first-ever application of RPYS (an objective, reproducible approach to study the early history of any scholarly activity) to pain research, infant pain management appears rooted in the scientific rationale for neonatal pain perception, randomized trials of opioid anesthesia/analgesia, and studies describing the facial expressions and crying activity following heel-lance procedures in newborns.

## KEYWORDS

analgesia, anesthesia, bibliometrics, cited references analysis, infant-newborn, nociception, pain, reference publication year spectroscopy (RPYS)

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## 1 | INTRODUCTION

Although infant pain was recognized in ancient history and even into the 17th century,<sup>1</sup> the emerging reliance on scientific methodology and prevailing scientific theories in the late 19th and 20th centuries resulted in an almost universal denial of pain perception in infants.<sup>2</sup> From a historical review, Rodkey and Pillai Riddell<sup>2</sup> found that this erroneous conclusion was reached because of the Darwinian view of children as less evolved beings, extreme reliance on null hypothesis testing from experimental findings (without considering the biases inherent in formulating those hypotheses), the behaviorism paradigm in psychology which viewed the infant from a mechanistic perspective, and an increasing emphasis on brain and nervous system development (often viewed through the colored lens of adult brain function).

From an analysis of all the articles listed in Medline, Gaurdiola and Banos<sup>3</sup> noted significant increases in the numbers of articles published on pediatric pain during the decade 1981-1990. The number of articles devoted to neonatal pain increased fourfold and articles related to infant pain increased threefold during the same period.<sup>3</sup> Subsequent analysis of articles on neonatal pain published from 1965 to 1999 showed very few publications from 1965 to 1985, but increased interest in this topic after 1985.<sup>4</sup> Most of this research came from the United States (38.6%), Canada (14.2%), and UK (13.3%), mainly related to infant colic (20.4%), general neonatal pain (13.6%), and procedural pain (13.4%).<sup>4</sup>

Clinical research in the 1980s seemed to overcome the denial of infant pain that was entrenched in medical practice and experimental science for over a century, thus opening the door to infant pain management. This paper seeks to discover the historical roots of infant pain management, but instead of taking the historical thematic approach by Rodkey & Pillai Riddell,<sup>2</sup> or the descriptive approach by Banos et al,<sup>4</sup> we used quantitative bibliometric methods to identify the published literature and to evaluate its relative importance in this field.

Bibliometrics as a quantitative method is not only useful for research assessment purposes but also for analyzing the history of science.<sup>5</sup> Which early works are still alive in more recent publications in the form of frequently cited references and are most important for the evolution of this research field? Questions regarding the historical

context of research topics can be answered by using a bibliometric method named "reference publication year spectroscopy" (RPYS),<sup>6,7</sup> readily performed using the program CitedReferencesExplorer (CRExplorer).<sup>8-10</sup>

Reference publication year spectroscopy changes the perspective of citation analysis from a times cited to a cited reference analysis.<sup>11</sup> RPYS assumes that the output of research (publications in most of the cases) is filled in a database accompanied by the references cited in their publications. This database can be analyzed statistically with regard to the publications most relevant for their specific field of research. Whereas individual scientists may judge the origins of their research field more or less subjectively, the overall community might deliver a more objective picture.<sup>12</sup> Researchers active in the field effectively "vote" by the references they cite, to identify publications most important for the evolution of their research field.

Reference publication year spectroscopy utilizes the following observation: Analysis of the publication years of the references cited by all papers in a specific research field (ie, analysis of the reference publication years, RPYs) shows that early RPYs are not equally represented. Some RPYs occur more frequently among the cited references than others. These RPYs appear as pronounced peaks in the distribution of the referenced publication years (ie, the RPY spectrogram). The peaks are frequently based on single early publications which have been referenced very often compared to other early publications. These publications are of special significance to the research field in question, since they often represent its origins and intellectual roots.<sup>13</sup> Several publications have applied the RPYS analysis in recent years to examine the origins of research fields in multiple disciplines.<sup>13-17</sup> Therefore, we performed a bibliometric analysis using RPYS to examine the historic origins of infant pain management.

## 2 | Methods

This analysis was based on all papers published in scientific journals related to the research on pain management in infants, identified using the search strategy listed in Table 1. The Web of Science (WoS, Clarivate Analytics) search query combined the infant-related synonyms (search #1) with the pain-related synonyms (search #2) and

**TABLE 1** Search strategy for infant pain publications

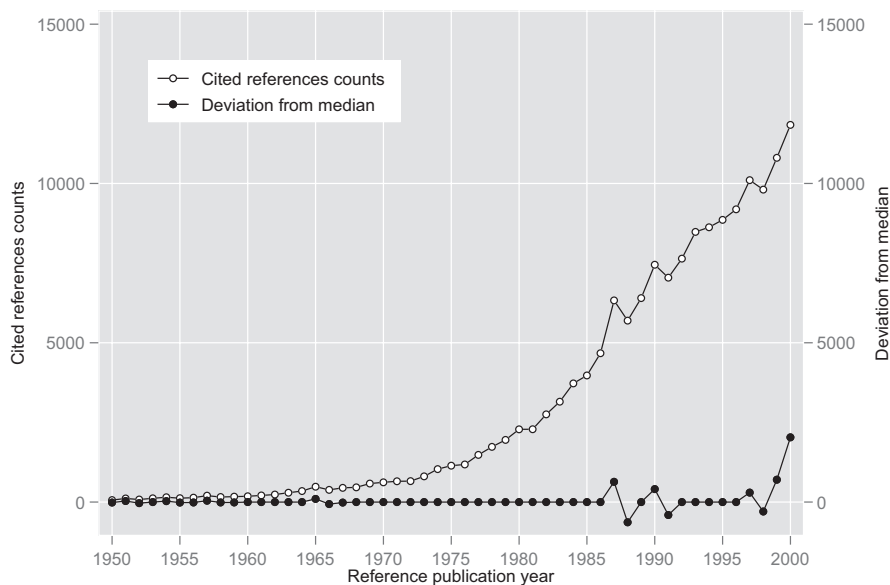
# 1	782 736	TOPIC: ((baby OR babies OR infant OR infants OR infancy OR neonat* OR newborn OR newborns OR perinatal))
# 2	5 091 425	TOPIC: ((pain OR painful OR stress OR stressful OR distress OR discomfort OR aversive OR hurt OR hurtful OR injury OR injuries OR nociception OR suffer* OR surgery OR surgical OR trauma* OR "skin breaking"))
# 3	430 878	TOPIC: ((analgesia OR analgesic OR anesthesia OR anesthetic OR morphine OR morphines OR opioid OR opioids OR "pain management" OR "pain relief"))
# 4	9280	#3 AND #2 AND #1

the analgesia or anesthesia-related synonyms (search #3) using the Boolean operator “AND,” resulting in 9280 publications (search #4). We applied WoS topic searching which implies selecting the search terms listed in our search query (see Appendix S1) within titles, abstracts, and keywords. The WoS search was based on the citation indexes SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC including all publication years, and our WoS search query retrieved all papers back to 1950 as the first publication year. The date of this search was December 17, 2019. These papers and their cited references were downloaded from the WoS database.

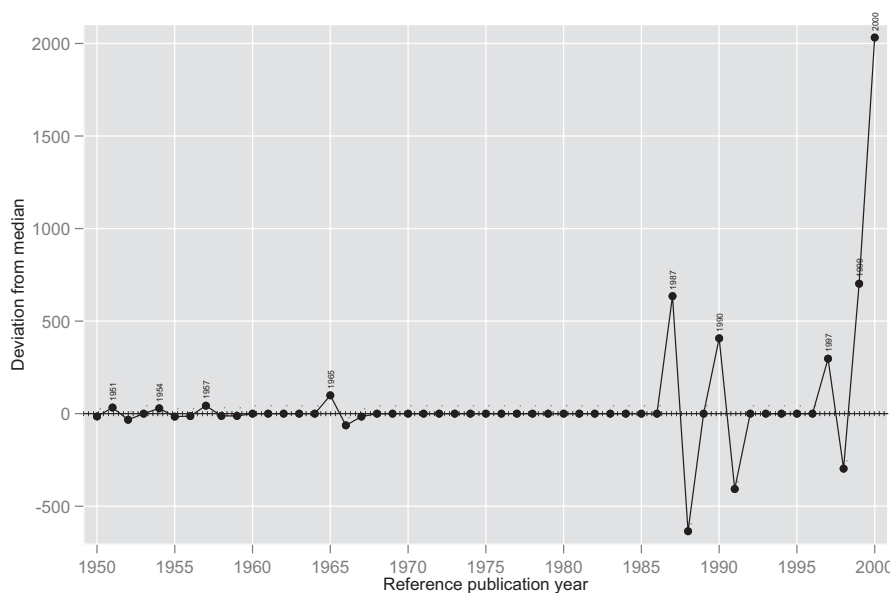
Manual selection based on content analysis of almost 9000 papers is clearly impractical. Also, every research topic contains gray areas making clear assignments questionable. Our information retrieval experiences have shown that getting complete and clean results by search queries is highly unlikely. However, we practiced

an iterative query optimization approach by identifying nonrelevant papers and by excluding the search terms which retrieve these papers. One advantage of RPYS is that it is not overly sensitive to the completeness and/or precision of the publication sets analyzed.

The download files were imported in the CRExplorer ([www.crexplorer.net](http://www.crexplorer.net)) for further processing.<sup>8,10</sup> The data import was restricted to the RPYs 1801 to 2000 to focus on historical roots from this period (89,099 cited references from 8697 publications). RPYS utilizes the principle that high peaks or deviations are hints to important publications in a research field: thus, the peaks in early RPYs point to the historical roots of the field or landmark publications. If the peak is very high for RPY  $t$  (and has a positive value for the number of cited references), many cited references from the publication set used will fall on RPY  $t$ , as compared to the median number of cited references based on the RPY period from  $t - 2$  to  $t + 2$ . In this study, we used the deviation from the 5-year median including ( $t - 2$ ;  $t - 1$ ;  $t + 1$ ;  $t + 2$ ).



**FIGURE 1** Number of cited references (open circles —○—) and median deviations of the cited references (closed circles —●—). The peaks with positive values show each reference publication year (RPY) with a significantly greater number of cited references than the bordering 2 y before and after it. This figure focuses on the years from 1950 to 2000



**FIGURE 2** Median deviations of the cited references. The peaks (with positive values) show cited reference years with a significantly greater number of cited references than bordering 2 y. This figure focuses on the years 1950 to 2000

The deviation from the 5-year median provides a curve smoother than the one based on cited references counts. Peaks in the data can be identified more easily than with the curve based on cited references counts, since each year is compared with its adjacent years.

In an initial historical analysis, Tukey's fences<sup>18</sup> were added to the median deviation (Figure 1) to support the identification of the most important peaks. Important peaks were then flagged based on the interquartile range of the median deviations<sup>15,19</sup> (Figure 2).

The contributions that were referenced very frequently for many years after their publication were thought to be landmark papers. To identify landmark publications, Thor et al had introduced the indicator  $N\_TOP10$ ,<sup>9,19</sup> which is the number of citing years in which a cited publication belongs to the top 10% of the most frequently referenced publications.<sup>19</sup> The most influential publications in any research field would thus be identified by the higher number of years in which those publications belonged to the top 10% most frequently referenced publications.<sup>13,17,19</sup>

### 3 | RESULTS

This RPYS analysis was based on 8697 papers containing 86,268 cited references. Reduction in number of cited references (from 89,099 to 86,268) resulted from using the clustering and merging functionalities of CRExplorer to clean the cited references dataset by removing duplicates or reference variants of the same cited publication. Thus, 2831 cited references were merged in the process of disambiguation (Table 2). Figure 1 shows the number of cited references (white dots) and deviation of the number of cited references in one RPY ( $t$ ) from the number of cited references in the bordering 2 years before ( $t - 2$ ) and after ( $t + 2$ ) this RPY. The cited references counts (Figure 1) and their deviations from median (Figures 1 and 2) comprise the total number of references in the particular reference publication years that were cited by the papers in our set. For example, there are about 6000 references in the RPY 1987 that were cited by the 8697 papers in our set. The peaks in the RPYS graph frequently result from a few highly cited publications.

### 3.1 | Publications associated with peak citation years

Two publications from each of the years responsible for the highest peaks in Figure 2 (1951, 1954, 1957, 1965, 1987, 1990, 1997, 1999, and 2000) are listed in Table 3. Besides the bibliographic information, this table shows the number of occurrences (in other words, how often these publications were cited by the papers dealing with infant pain management) in absolute and relative terms (as a percentage of the total number of occurrences in that RPY).

The cited references peaks in Figure 2 suggest an early phase from 1951 to 1965 and a later phase from 1987 to 2000. Publications in the later phase showed higher absolute numbers of cited references than in the early phase (Mean  $\pm$  SD:  $178 \pm 101$  vs  $24.4 \pm 22.8$ ,  $P < 0.0001$ ), yet the later cited references constituted much smaller percentages of the cited literature in infant pain publications within their respective RPYs ( $2.1 \pm 1.9\%$  vs  $9.6 \pm 3.5\%$ ,  $P < 0.0001$ ). Lowry et al<sup>20</sup> describe a method for measuring proteins with the Folin phenol reagent after alkaline copper treatment. The WoS database shows that this is the most-cited paper of all times with about 340 000 citations, and therefore, it probably appears in every cited reference analysis in the life sciences.

In the *early phase*, Berkowitz and Greene<sup>21</sup> describe their clinical experience with spinal anesthesia in 350 children, which included only one infant (a 1-year-old boy with incarcerated hernia). Ruston<sup>22</sup> pioneered the use of epidural anesthesia in infants and small children—his report describes 44 patients, mostly infants with pyloric stenosis but also included some critically ill newborns. Beecher and Todd<sup>23</sup> surveyed the anesthesia and surgery outcomes for about 600 000 patients from 10 university hospitals and reported disproportionately high anesthesia-related deaths in children below 10 years and adults above 60 years. In 1957, Levine demonstrated that a mild-stressor in neonatal rats promoted adaptation to social and physiological stress in adulthood<sup>24</sup>; whereas Holliday and Segar<sup>25</sup> described a formula for calculating the fluid and electrolyte needs of children based on their caloric requirements. In 1965, Melzack and Wall<sup>26</sup> described their seminal gate

**TABLE 2** Exported, imported, and disambiguated datasets

	Exported dataset from Web of Science	Imported dataset from Web of Science	Disambiguated dataset
Number of nondistinct cited references	338 984	159 659	
Number of distinct cited references		89 099	86 268
Minimum reference publication year	1007	1801	1801
Maximum reference publication year	2020	2000	2000
Number of publications	9280	8697	8697
Minimum publication year	1950	1950	1950
Maximum publication year	2019	2019	2019

Note: Exported dataset: papers downloaded from the WoS.

Imported dataset: pre-2000 papers imported by the CRExplorer.

Disambiguated dataset: cited papers after merging the various reference variations.

Cited references	Cited references counts (absolute)	Cited references counts (percent in that RPY)
1951		
Lowry OH, et al J Biol Chem 1951; 193:265-275	17	15%
Berkowitz S, Greene BA. Anesthesiology 1951; 12:376-387	10	9%
1954		
Ruston FG. Can Anaesth Soc J 1954; 1:37-44	12	8%
Beecher HK, Todd DP. Ann Surg 1954; 140:2-35	11	7%
1957		
Levine S. Science 1957; 126:405	16	8%
Holliday MA, Segar WE. Pediatrics 1957; 19:823-832	11	6%
1965		
Melzack R, Wakk PD. Science 1965; 150:971-979	73	15%
Way WL, et al Clin Pharmacol Ther 1965; 6:454-461	45	9%
1987		
Anand KJS, Hickey PR. N Engl J Med 1987; 317:1321-1329	381	6%
Anand KJS, et al Lancet 1987; 1:243-248	300	5%
1990		
Grunau RVE, et al Pain 1990; 42:295-305	79	1%
Anand KJS, et al Anesthesiology 1990; 73:661-670	76	1%
1997		
Taddio A, et al Lancet 1997; 349:599-603	262	3%
Merkel SI, et al Pediatr Nurs 1997; 23:293-297	135	1%
1999		
Anand KJS, et al Arch Pediatr Adolesc Med 1999; 153:331-338	144	1%
Ikonomidou C, et al Science 1999; 283:70-74	142	1%
2000		
Lemons JA, et al Pediatrics 2000; 105:454-461	138	1%
Anand KJS, Scalzo FM. Biol Neonate 2000; 77:69-82	123	1%

Note: The two most-cited references were selected in each year, and percentages are calculated on the base of the total number of cited references in that 1 y.

**TABLE 3** Cited references with the highest number of occurrences in reference publication years (Corresponding to the highest peaks in Figure 2)

control theory of pain, which laid the foundations for many areas of pain research, whereas Way et al<sup>27</sup> found that newborns are more sensitive to the respiratory depressant effects of morphine using infant body plethysmography and endtidal CO<sub>2</sub> sampling. All

these are classic articles but only the latter two have relevance to the field of infant pain management.

The *later phase* starts in 1987 with Anand et al<sup>28</sup> describing a placebo-controlled randomized trial of fentanyl anesthesia in preterm

newborns undergoing surgical ligation of patent ductus arteriosus (PDA), showing reduced stress responses and fewer complications in the fentanyl group. Later that year, Anand and Hickey<sup>29</sup> synthesized the available evidence for pain perception in human newborns, therein outlining the scientific frameworks for its assessment, management, and long-term effects. In 1990, Grunau et al<sup>30</sup> described the facial expressions and cry characteristics of term newborns undergoing an invasive procedure (intramuscular injection) and two noninvasive procedures, whereas Anand et al<sup>31</sup> reported the hormonal-metabolic stress responses of neonates undergoing cardiac surgery, partially accentuated among those who died after surgery. In 1997, Taddio et al<sup>32</sup> found that infants circumcised without pain relief at birth had significantly greater responses to vaccination pain at 4-6 months postnatal age, compared to either uncircumcised infants or those receiving a topical anesthetic cream for circumcision. Merkel et al<sup>33</sup> also published the FLACC\* behavioral scale in 1997, designed for measuring postoperative pain in children aged 2 months to 7 years.

In 1999, Anand et al<sup>34</sup> published results from their NOPAIN randomized trial suggesting the beneficial effects of morphine analgesia compared to midazolam sedation or placebo in mechanically ventilated preterm neonates, whereas Ikonomidou et al<sup>35</sup> found widespread apoptotic neurodegeneration in the brains of 7-day-old infant rats given high doses of NMDA receptor antagonists. By the year 2000, professional bodies could no longer ignore the accumulating evidence for neonatal pain. Finally, the American Academy of Pediatrics and the Canadian Paediatric Society released a statement to increase awareness that neonates do experience pain, provide a physiological basis for pain assessment and management, recommended reducing the exposure of neonates to noxious stimuli, and treating neonatal pain with effective and safe interventions.<sup>36</sup> Based on findings from Ikonomidou et al, Anand & Scalzo (2000) hypothesized that repetitive neonatal pain may lead to excitotoxic cell death from NMDA receptor hyperexcitability, whereas the lack of adequate NMDA receptor stimulation from maternal separation or NMDA receptor blockade may promote apoptosis in the neonatal brain.<sup>37</sup>

Although the two most popular cited references from the peaks in Figure 2 may give a flavor of the research developments related to infant pain management, they do not offer a clear identification of which studies led to sustained developments in the field. This analysis also identified publications with little (eg, Beecher and Todd<sup>23</sup>) or no relevance (eg, Holliday and Segar<sup>25</sup>) to infant pain management while failing to recognize other especially important contributions (see below).

### 3.2 | Identification of landmark publications

In a second historical analysis, we sought to identify the contributions that were referenced very frequently over many years after publication. For infant pain management, Table 4 lists the most influential publications in the order of their impact.

The five most influential papers appeared to be: (a) a randomized trial of fentanyl anesthesia in preterm neonates undergoing PDA ligation,<sup>28</sup> (b) a narrative review synthesizing the scientific evidence for neonatal pain,<sup>29</sup> (c) a detailed analysis of facial expressions and crying activity following a heel-lance for blood sampling,<sup>38</sup> (d) the higher incidence of respiratory complications in preterm infants (11/33, 33%) vs term infants (1/38, 2.6%) after inguinal herniotomy,<sup>39</sup> and (e) greater heart rate responses and duration of crying after heel-lance in 10 male and 10 female newborns compared to their responses to tactile stimuli.<sup>40</sup> Other landmark papers<sup>30,31,41-57</sup> and their brief summaries are included in Table 4.

## 4 | DISCUSSION

Retrospective evaluations of the historical role and scientific importance of previously published research is often fraught with subjective bias and misrepresentation, and often leads to contested scientific claims.<sup>41</sup> To establish the historical context of published research on infant pain management, we used a bibliometric method named "RPYS." This novel approach may avoid some of the subjectivity associated with the comparative evaluations of individual research studies in narrative reviews, now increasingly considered as a significant flaw within the peer review system.<sup>42</sup>

The citation peaks in Figure 2 were noted from RPYs in an early (1951-1965) and later phase (1987-2000) and the two most-cited papers from these peaks were listed in Table 3. However, when we performed the N\_TOP10 data analysis to identify the landmark publications, other highly relevant papers were published before 1987. These included, for example, Steward<sup>39</sup>; Owens and Todt<sup>40</sup>; Abajian et al<sup>43</sup>, McGrath et al,<sup>48</sup> and others listed in Table 4. Therefore, 1982-1992 appears to be a golden decade for infant pain research, since all landmark papers were published during this period.

Earlier papers set the context for infant pain management, with David Steward observing that preterm infants had more frequent postoperative respiratory complications following general anesthesia than term infants,<sup>39</sup> and Chris Abajian<sup>43</sup> providing an alternative using spinal anesthesia. Following acute neonatal pain, Owens and Todt<sup>40</sup> established a need for pain relief based on tachycardia and crying associated with a heel-lance, whereas Field & Goldson<sup>44</sup> showed that non-nutritive sucking could provide such relief. In 1984, Mark Owens<sup>45</sup> discussed the conceptual and methodological issues related to pain in infancy, proposing parallel studies on emotion and pain in infants, which did not emerge from our analysis. RPYS did not select this review article possibly because it was not referenced frequently, or perhaps because it dealt with conceptual and methodological issues, but not infant pain management. The following year, Anand et al<sup>46</sup> reported that neonates undergoing surgery have accentuated stress responses, at least partly explained by Fitzgerald and Koltzenburg's<sup>47</sup> experiments showing delayed functional development of descending inhibitory pathways in the dorsolateral

\*FLACC assesses five categories of pain behaviors: Facial expression, Leg movement, Activity, Cry, Consolability.

**TABLE 4** Landmark publications for research on pain management in infants

Cited references	Brief summary	Absolute number of years <sup>a</sup>	Percentage of years since publication <sup>b</sup>
1. Anand KJS, et al Lancet 1987; 1:243-248	Randomized trial of fentanyl anesthesia in preterm neonates undergoing PDA ligation	33	100%
2. Anand KJS, Hickey PR. N Engl J Med 1987; 317:1321-1329	Narrative review synthesizing the scientific evidence for neonatal pain	32	97%
3. Grunau RVE, Craig KD. Pain 1987; 28:395-410	Detailed analysis of facial expressions and crying activity following a heel-lance for blood sampling	31	94%
4. Steward DJ. Anesthesiology 1982; 56:304-306	Higher incidence of respiratory complications in preterm infants (11/33, 33%) vs term infants (1/38, 2.6%) after inguinal herniotomy	30	79%
5. Owens ME, Todt EH. Pain 1984; 20:77-86	Greater heart rate responses and duration of crying after heel-lance in 10 male and 10 female newborns compared to their responses to tactile stimuli	29	81%
6. Blass E, et al Pharmacol Biochem Behav 1987; 26:483-489	Original experiments showing oral sucrose decreases the responses to pain and stress in 10-d-old rats	29	88%
7. Bosenberg AT, et al Anesthesiology 1988; 69:265-269	Cadaveric, animal, and human studies to achieve thoracic epidural anesthesia by inserting a catheter via the sacral hiatus in infants aged 4 wk to 5 mo	29	91%
8. Anand KJS, et al Brit Med J (Clin Res Ed) 1988; 296:668-672	Randomized placebo-controlled trial of halothane anesthesia showing reduced stress responses in term newborns	29	91%
9. Abajian JC, et al Anesth Analg 1984; 63:359-362	Early clinical experience with spinal anesthesia in 78 high-risk term and preterm infants	28	78%
10. McGrath PJ, et al Adv Pain Res Ther, 1985; 9:395-402	Assessment of pain behaviors following circumcision in 30 boys (1-7 y old) to validate the CHEOPS pain score	28	80%
11. Anand KJS, Carr DB. Pediatr Clin North Am 1989; 36:795-822	Neuroanatomy, neurophysiology, and neurochemistry of pain/analgesia in newborns and children review	28	90%
12. Blass EM, Hoffmeyer LB. Pediatrics 1991; 87:215-218	Observational study showing the effectiveness of sucrose analgesia for newborns undergoing heel-lance (n = 24) or circumcision (n = 30)	28	97%
13. Anand KJS, Hickey PR. N Engl J Med 1992; 326:1-9	Randomized placebo-controlled trial of high-dose opioid anesthesia and analgesia for newborns undergoing cardiac surgery showing reduced stress responses and improved clinical outcomes	28	100%
14. Anand KJS, et al J Pediatr Surg 1985;20:41-8	Observational study of the hormonal-metabolic stress responses in 33 infants (26 term, 7 preterm) subjected to surgery	27	77%
15. Fitzgerald M, Koltzenburg M. Dev Brain Res 1986; 389:261-270	Experimental evidence showing the delayed functional development of descending inhibition from the brainstem until days 10-12 after birth in Wistar infant rats	27	79%
16. Welborn LG, et al Anesthesiology 1990; 72:838-842	Randomized trial showing no differences in postoperative apnea in 36 former preterm infants receiving general vs spinal anesthesia for inguinal hernia repair	27	90%
17. Field T, Goldson E. Pediatrics 1984; 74:1012-1015	Observation that non-nutritive sucking attenuates both physiologic arousal and behavioral distress in neonates during a painful procedure	26	72%
18. Koehntop DE, et al Anesth Analg 1986; 65:227-232	Pharmacokinetics of fentanyl in 14 neonates undergoing major surgical procedures	26	76%
19. Johnston CC, Strada ME. Pain 1986; 24:373-382	Heart rate, crying activity, body movements, and voice spectrographs of 14 healthy infants (2 or 4 mo old) during routine immunizations to characterize the multidimensional response to acute pain	26	76%

(Continues)



TABLE 4 (Continued)

Cited references	Brief summary	Absolute number of years <sup>a</sup>	Percentage of years since publication <sup>b</sup>
20. Fitzgerald M, et al <i>Dev Med Child Neurol</i> 1988; 30:520-526	Postnatal development of the cutaneous flexor reflex in preterm infants and newborn rat pups defining their transition from sensitization to habituation related to the neurophysiological maturation of their descending inhibitory pathways	26	82%
21. Blass EM, Fitzgerald E. <i>Pharmacol Biochem Behav</i> 1988; 29:9-13	Demonstrated the calming and analgesic effects of intraoral milk in 10-d-old rats	26	82%
22. Fitzgerald M, et al <i>Pain</i> 1989; 39:31-36	Documented hyperalgesia in the newborn skin injured by multiple heelsticks and its reversal with a topical anesthetic cream	26	84%
23. Grunau RVE, et al <i>Pain</i> 1990; 42:295-305	Facial expressions and cry characteristics of term newborns following intramuscular injections and two noninvasive procedures	26	87%
24. Anand KJS, et al <i>Anesthesiology</i> 1990; 73:661-670	Stress responses of babies undergoing cardiac surgery, partially accentuated among those who had died after surgery	26	87%

Note: The table lists only those publications with more than 25 y of being cited frequently.

<sup>a</sup>Publications are listed in order of the absolute number of years in which that publication belonged to the top 10% most frequently referenced publications.

<sup>b</sup>Because the research published in earlier years was available for being referenced over longer periods of time, we also calculated the percentage of the years in which that publication remained within the top 10% of most frequently referenced publications.

funiculus of newborn rats. Also in 1985, McGrath et al<sup>48</sup> reported initial results from using the CHEOPS pain scale in 1- to 7-year-old children, whereas Johnston and Strada<sup>49</sup> expanded on the findings of Owens & Todt, by describing the patterns of neonatal pain responses from a multidimensional perspective and setting the stage for clinical assessments of *neonatal pain*.

In 1981, Robinson and Gregory<sup>50</sup> had published their experience with fentanyl anesthesia (30–50 µg/kg) for PDA ligation in preterm neonates and Koehntop et al<sup>51</sup> had used similar doses (25–50 µg/kg) for pharmacokinetic studies of fentanyl in term and preterm neonates. In the first randomized placebo-controlled trial of neonatal anesthesia, Anand et al<sup>28</sup> found that fentanyl reduces the responses of preterm babies to the stress of PDA ligation even at lower doses (10–12 µg/kg). The media controversy that followed this publication ensured that the anesthetic needs of newborns could no longer be ignored.<sup>52</sup> To bolster their argument that neonatal stress responses may be triggered by surgically induced pain in the setting of inadequate anesthesia, Anand and Hickey<sup>29</sup> reviewed evidence for the developing anatomical and functional requirements, neurochemical systems, physiological changes, behavioral responses, as well as the potential long-term effects of painful experiences in preterm and term neonates. Decades later, this publication was listed as one of the 20 game-changers in the field of anesthesia.<sup>53</sup>

Subsequent publications contributed to the burgeoning medical and public interest in infant pain. Grunau and Craig's<sup>38</sup> detailed observations of the facial actions and crying patterns following acute painful stimuli were foundational to the methods for infant pain assessment showing that awake-alert infants have more robust facial expressions whereas sleeping infants show the least facial reactions

and longest latency to cry. Elliot Blass's experiments on the calming and analgesic effects of oral sucrose<sup>54</sup> and breastmilk in rats<sup>55</sup> were again foundational for developing these novel nonpharmacologic approaches for infant pain management.<sup>56–58</sup> Adrian Bosenberg's<sup>59</sup> careful work from South Africa still remains as the basis for widespread use of caudal epidural anesthesia today!

In a comparative study of human infants and neonatal rat pups, Maria Fitzgerald et al<sup>60</sup> demonstrated the parallel development of the dorsal cutaneous flexor reflex as a measure of cutaneous sensitivity and pain threshold. Another landmark article was the first clinical demonstration of injury-associated primary hyperalgesia in preterm newborns, which was reversed by local topical anesthesia in a nonrandomized placebo-controlled study.<sup>61</sup> Maria Fitzgerald and her group made monumental contributions to our understanding of infant pain mechanisms,<sup>62,63</sup> but these and other translational studies<sup>64–66</sup> were not identified in the RPYS analysis probably because of its focus on infant pain management.

As pain perception in newborns was more widely accepted, the focus shifted toward testing the comparative efficacy of various therapeutic approaches. Thus, landmark publications from the 1990s mostly described randomized comparisons of different approaches for neonatal anesthesia/analgesia. Although Welborn et al<sup>67</sup> found no differences in postoperative apnea in former preterm infants randomized to general vs spinal anesthesia, this study design was used as a template for several other multicenter anesthesia trials comparing neonatal outcomes.<sup>68,69</sup> Blass and Hoffmeyer<sup>70</sup> reported two randomized placebo-controlled trials showing the effectiveness of sucrose analgesia for heel-lance and circumcision procedures. Having found accentuated stress responses in infants undergoing cardiac



surgery,<sup>31</sup> Anand and Hickey performed a randomized comparison of halothane-morphine vs high-dose opioid anesthesia and reported a reduced mortality as well as fewer postoperative complications in those given opioid anesthesia and analgesia.<sup>71</sup> The cumulative evidence from these and other ensuing studies have established the anesthetic and analgesic management of infants on firm scientific footing for the current-day medical and surgical practices.

The results of this analysis must be interpreted in terms of its limitations. RPYS relies on the “popularity” of a reference being cited in subsequent research, it measures impact but not scientific quality. Other parts of scientific quality are accuracy and importance, which cannot be measured by cited reference analyses. Note that many reasons exist why authors cite publications,<sup>72</sup> thus introducing a lot of “noise” into the data (this is why RPYS focuses on the cited references peaks). Other articles (like Holliday and Segar<sup>25</sup>) that were not related to infant pain management showed up as a peak in their respective RPYs, perhaps because of specific keywords for their coding in the WoS database.

The WoS database contains the articles published from 1900 and included abstracts only from 1990 onwards. Despite this, the RPYS identified earlier publications because they were cited frequently in the publications downloaded from WoS. Another concern is that papers published earlier were available for being cited for longer periods than those published later, but this is consistent with identifying the “historical” roots of this field and acknowledging that later research was designed with the insights gained from earlier studies. Nevertheless, Table 4 also lists the percentage of years in which a publication remained within the top 10% of most frequently referenced publications. Ongoing refinements in the RPYS approach may address or adjust for other such limitations.

Despite these limitations, the RPYS provides an objective and reproducible method to study the early history of any scholarly activity. We present the first-ever application of this technique to the field of pain research, based on our search identifying almost 8700 unique publications and analyzing over 86,000 cited references. This analysis identified and ranked 24 landmark publications to illustrate the historical roots of infant pain management. From our analyses, infant pain management appears rooted in the scientific rationale for neonatal pain perception, a randomized trial of fentanyl anesthesia in preterm neonates, and studies describing the facial expressions and crying activity following heel-lance procedures in newborns. Expanding our search strategy to focus on infant pain per se may reveal the “historical roots” of infant pain research and include the contributions of other leaders in the field. Epochal and exciting developments have occurred in the field of infant pain management over the past four decades, giving rise to a vibrant and growing scientific community, continually refreshed by new talented researchers and students equipped with much greater creativity and courage to tackle the most important questions.

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#### CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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