BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2016, **119**, 512–519 Doi: 10.1111/bcpt.12609

Intravenous Lipid Emulsion as an Antidote for the Treatment of Acute Poisoning: A Bibliometric Analysis of Human and Animal Studies

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(Received 18 December 2015; Accepted 5 April 2016)

Abstract: In recent years, there has been increasing interest in the role of intravenous lipid formulations as potential antidotes in patients with severe cardiotoxicity caused by drug toxicity. The aim of this study was to conduct a comprehensive bibliometric analysis of all human and animal studies featuring lipid emulsion as an antidote for the treatment of acute poisoning. The Scopus database search was performed on 5 February 2016 to analyse the research output related to intravenous lipid emulsion as an antidote for the treatment of acute poisoning. Research indicators used for analysis included total number of articles, date (year) of publication, total citations, value of the *h*-index, document types, countries of publication, journal names, collaboration patterns and institutions. A total of 594 articles were retrieved from Scopus database for the period of 1955–2015. The percentage share of global intravenous lipid emulsion research output showed that research output was 85.86% in 2006–2015 with yearly average growth in this field of 51 articles per year. The USA, United Kingdom (UK), France, Canada, New Zealand, Germany, Australia, China, Turkey and Japan accounted for 449 (75.6%) of all the publications. The total number of citations for all documents was 9,333, with an average of 15.7 citations per document. The *h*-index of the retrieved documents for lipid emulsion research as antidote for the treatment of acute poisoning was 49. The USA and the UK achieved the highest *h*-indices, 34 and 14, respectively. New Zealand produced the greatest number of documents with international collaboration (51.9%) followed by Australia (50%) and Canada (41.4%) out of the total number of publications for each country. In summary, we found an increase in the number of publications in the field of lipid emulsion after 2006. The results of this study demonstrate that the majority of publications in the field of lipid emulsion were published by high-income countries. Researchers from institutions in the USA led scientific production on lipid emulsion research. There is an obvious need to promote a deeper engagement through international collaborative research projects and funding mechanisms.

Intravenous lipid formulations have been used for many years to provide parenteral nutritional support in hospitalized patients. In recent years, there has been increasing interest in its role as a potential antidote in patients with severe cardiotoxicity caused by drug toxicity. Systemic toxicity arising from local anaesthetic agents was first recognized in the late 1970s, was characterized by electrocardiographic abnormalities, cardiovascular collapse, decreased level of consciousness, coma and seizures and carried a high mortality rate despite conventional resuscitation attempts [1–4]. Data from animal studies have consistently shown that intravenous lipid emulsion may reduce cardiac toxicity after various local anaesthetic agents and reduce mortality [5,6].

Several clinical case reports showed that urgent administration of intravenous lipid emulsion to patients with local anaesthetic systemic toxicity has ameliorated electrocardiographic and blood pressure abnormalities when conventional resuscitation measures have failed [7,8]. The administration of intravenous lipid emulsion is now included in international resuscitation guidelines for patients with local anaesthetic systemic toxicity. For example, the American Heart Association and the European Resuscitation Council currently advise bolus intravenous administration followed by repeated bolus administration and, depending upon response, a maintenance intravenous infusion [9,10].

Several mechanisms for the antidote properties of intravenous lipid emulsion have been proposed, including preferential distribution of lipid-soluble drugs into a circulating lipid phase, thereby reducing tissue drug concentrations [11]. There may also be a direct inotropic effect and restoration of myocardial contractility due to improved fatty acid oxidative metabolism [12,13].

A number of different drugs may cause fatal cardiotoxicity in the context of intentional overdose, including certain antidepressants [14–18]. This has stimulated interest in the possibility that urgent intravenous lipid emulsion may be effective in the resuscitation of cardiotoxicity associated with a broader range of drugs. A positive clinical response has been reported

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in around half of all published cases of non-anaesthetic toxicity, but too little data are available to be sure about whether routine administration in this setting will improve patient outcome [8]. Intravenous lipid emulsion is increasingly being considered in patients with severe life-threatening cardiotoxicity, especially where the response to standard resuscitation measures has been poor, and the expected mortality risk is high. There is a need for systematic data collection to gain a clearer understanding of patient outcome after lipid administration for non-anaesthetic drug toxicity [19].

Although bibliometric analyses are becoming widely accepted as a means of evaluating scientists and/or research in certain fields, this is the first quantitative and qualitative bibliometric analysis of lipid emulsion research as an antidote for the treatment of acute poisoning. Quantitative and qualitative bibliometric analysis of the existing literature as an indicator of scientific research performance has become a common type of study in the toxicology field [20–28]. Bibliometric indicators can assess the available literature in evaluating the research activity, a research area and an institution at a regional, national or global level, thereby providing methods for better allocation of resources. The aim of this study was to conduct a comprehensive bibliometric analysis of all human and animal studies featuring lipid emulsion research as an antidote for the treatment of acute poisoning.

Methods

The Scopus database search was performed on 5 February 2016 to analyse the research output related to intravenous lipid emulsion as an antidote for the treatment of acute poisoning, performed with the advanced search feature. This database was chosen as it covers a large number of journals compared to other databases, including citation analysis, and most researchers target the journals indexed in Scopus database when publishing their work [29–31].

The search terms used to retrieve data were elected from previous review studies related to intravenous lipid emulsion [8,32–38]. The Scopus database search was conducted by applying the following keywords in the title and abstract for all the years up to 31 December 2015: (intralipid, lipid emulsion, lipid therapy, fat therapy, lipid resuscitation, lipovenous, fat emulsion, intravenous fat, fat infusion, fat injection, intravenous lipid, lipid infusion and lipid injection) AND (poison*, intoxication, antidot*, toxic*, resuscit*, emergency, overdose, rescue and arrest). We used wildcard characters to search for variations of a word using the asterisk (*) to make our search shorter and simpler. For example, when searching: entering 'poison*' in a search engine that offered wildcard character ability, results would be given for poison, poisons, poisonous and poisoning – briefly, any possible word that might begin with the six letters (i.e. 'poison'). Documents as errata and scientific research productivity in 2016 were excluded from analysis. Furthermore, documents in which the primary focus was not dealing with lipid therapy for acute poisoning such as research related to nutrition, endotoxin, formulation or chemistry were excluded.

Research indicators for the evaluation of research output in the field of lipid emulsion were used based on a method used previously by our team in similar bibliometric studies [20–23,39–42]. Research indicators that were used for analysis included total number of articles, date (year) of publication, total citations, value of the *h*-index, document types, country of publication, journal names, collaboration patterns and institutions. We considered only the ten top-ranked research indicators, and they were presented in rank order using the standard competition ranking (SCR). To measure the quality of the research published in the field of lipid emulsion, we used *h*-index and impact factors as bibliometric indicators for the evaluation. The *h*-index is a simple bibliometric indicator developed by Hirsch [43] in 2005 to measure both the productivity and citation impact of the publications. The definition of the *h*-index is that a country with an index of h has published h papers, each of this paper has at least h citations each [43]. The impact factor (IF) is obtained from the 2014 Journal Citation Reports® (Thomson Reuters, New York, NY, USA) [44] and is a measure of journal prestige and impact.

Ethical approval. In our institution, institutional review board (IRB) approval is not necessary for bibliometric studies and for databases that are publicly available. IRB approval was therefore not obtained. As such, all of the bibliometric analyses were conducted under an exemption from informed consent because this study did not involve any interactions with human participants [21,23,40].

Statistical analysis. The Statistical Package for Social Sciences (SPSS) software (SPSS version 15.0 for Windows; SPSS, Chicago, IL, USA) and Microsoft Excel version 2003 (Microsoft Corporation, Redmond, WA) were used for all statistical analyses. Only descriptive statistics were used, such as sum, average, frequencies and percentages. Pearson's correlation test was used to assess the correlation between time of research productivity and number of articles in areas of research interest. Two independent researchers (SZ and SA) extracted and screened articles for eligibility, and discrepancies were eliminated.

Results

Figure 1 shows the number of research publications on intravenous lipid emulsion during the period of 1955–2015. A total of 594 articles were retrieved from Scopus. The yearly average growth in this field was 9.74 articles per year. The percentage share of global intravenous lipid emulsion research output showed that research output was 85.86% in 2006–2015 with a yearly average growth in this field of 51 articles per year (fig. 1). The most common type of publications on lipid emulsion were original articles, accounting for 70.4% of the total studies. Reviews were the second most common type of document (13.1%), followed by letters to the editors (11.3%). The remaining 5.2% corresponded to other types of publications such as editorials, conference papers or notes. The first article indexed in Scopus database was published in 1955 by Brown *et al.* [45].

The research publications originated from 40 countries, indicating the international spread of lipid emulsion research as an antidote for the treatment of acute poisoning. Table 1 shows the top 10 countries ranked according to total number of publications of lipid emulsion literature in Scopus database published during the period of study. Table 1 demonstrates that the top 10 countries (USA, UK, France, Canada, New Zealand, Germany, Australia, China, Turkey and Japan) accounted for 449 (75.6%) of all the publications. 'Collaboration with other countries' refers to the number of other countries represented among authors who collaborated with authors from a particular country; we found that the USA, Canada and Australia achieved the highest collaboration with other countries

(17, 8 and 8 countries, respectively). New Zealand produced the greatest number of documents with international collaboration (51.9%) followed by Australia (50%) and Canada (41.4%) out of the total number of publications for each country (Table 1). The total number of citations for all documents was 9,333, with an average of 15.7 citations per document. The *h*-index of the retrieved documents for lipid emulsion research as an antidote for the treatment of acute poisoning was 49. The USA and the UK achieved the highest *h*-indices, 34 and 14, respectively.

The published outputs were retrieved from 286 different journals, representing an enormous range of disciplines. Table 2 shows the top 10 journals ranked according to total number of publications of lipid emulsion research literature in Scopus database, which accounted for 186 (31.3%) of all the publications. Thirty-one documents (5.2%) were published in *Anaesthesia and Analgesia*, 29 (4.9%) were published in *Anaesthesia* and 26 (4.4%) were published in *Clinical Toxicology*. The impact factors for journals containing top 10 cited lipid emulsion articles ranged from 1.052 to 6.312. Only one journal in the top 10 cited journals was without IF. Of the 594 retrieved documents, 196 were related to human beings. Of course, there was some overlap between results obtained for animals and human beings, particularly in reviews, commentaries or editorials. Two hundred and eleven publications on lipid emulsion were case reports or case series, accounting for 35.5% of the total documents. Areas of research interest of retrieved documents were mainly dealing with anaesthetic toxicity (272; 45.8%) followed by poisoning by cardiovascular medications such as calcium channel blockers or beta-blockers (138; 23.2%) and central nervous system medications such as antidepressants or antipsychotics (104; 17.5%). The remaining documents were about other poisonings such as organophosphate compounds, aluminium phosphide or glyphosate. There was a statistically significant correlation between year of publication and the number of articles in areas of research interest either articles dealing with anaesthetic toxicity or other cardiotoxins ($r = 0.34$; $p = 0.013$). This finding might indicate that researchers' interests continue in both areas of research in the last decade.

Table 3 shows the ten most cited documents in lipid emulsion research as an antidote for the treatment of acute poisoning, in descending rank order of citations received [5–7,37,46–51]. The total number of citations per document for the ten most cited papers ranged from 351 to 121 (Table 3). The impact factor for all journals containing top 10 cited lipid emulsion articles ranged from 3.089 to 13.215.

Total publication output during 1955–2015 came from 194 institutions spread among 40 countries. Table 4 shows the top 10 institutions ranked according to the total number of publications of lipid emulsion research literature in Scopus database published, which accounted for 144 (24.2%) of all publications. The most prolific institution was the University of Illinois at Chicago (USA), followed by Waikato Hospital (New Zealand). Among the top 10 institutions, six were in the USA. All the top institutions appeared in the top 10 ranking countries, except Finland.

Discussion

The results of this study explain how developments in this topic have progressed over time. It becomes obvious which countries, authors and institutions have made exceptional

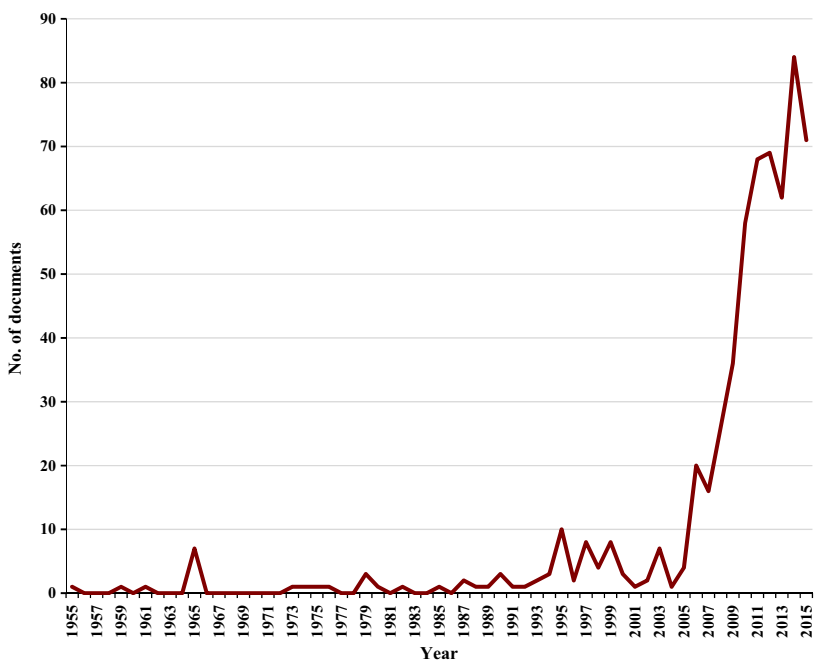

Fig. 1. Numbers of intravenous lipid emulsion research literature trends in Scopus database between 1955 and 2015.

Table 1.
Top 10 countries ranked according to total number of publications on lipid emulsion research in Scopus, published between 1955 and 2015.

SCR[1]	Country	Total articles included, n (%)	h-index	Collaboration with other countries	Articles with international collaboration, n (%)
1st	USA	198 (33.3)	34	17	32 (16.2)
2nd	UK	56 (9.4)	14	7	4 (7.1)
3rd	France	35 (5.9)	11	7	4 (11.4)
4th	Canada	29 (4.9)	12	8	12 (41.4)
5th	New Zealand	27 (4.5)	12	4	14 (51.9)
6th	Germany	24 (4.0)	9	3	3 (12.5)
6th	Australia	24 (4.0)	10	8	12 (50.0)
8th	China	21 (3.5)	8	1	5 (23.8)
9th	Turkey	18 (3.0)	3	0	0 (0.0)
10th	Japan	17 (2.9)	7	1	2 (11.8)

SCR, standard competition ranking.
[1]Equal countries have the same ranking number, and then, a gap is left in the ranking numbers.

Table 2.
Top 10 journals for lipid emulsion research literature in Scopus, published between 1955 and 2015

SCR[1]	Journal	Frequency (%)	IF[2]
1st	*Anaesthesia and Analgesia*	31 (5.2)	3.472
2nd	*Anaesthesia*	29 (4.9)	3.382
3rd	*Clinical Toxicology*	26 (4.4)	3.673
4th	*Journal of Medical Toxicology*	19 (3.2)	NA
4th	*Anaesthesiology*	19 (3.2)	5.879
6th	*American Journal of Emergency Medicine*	15 (2.5)	1.274
7th	*Regional Anaesthesia and Pain Medicine*	13 (2.2)	3.089
8th	*Critical Care Medicine*	12 (2.0)	6.312
9th	*Academic Emergency Medicine*	11 (1.9)	2.006
9th	*Journal of Veterinary Emergency and Critical Care*	11 (1.9)	1.052

SCR, standard competition ranking; NA, not available; IF, impact factor.
[1]Equal journals have the same ranking number, and then, a gap is left in the ranking numbers.
[2]The impact factor was reported according to the Institute for Scientific Information (ISI) journal citation reports (JCR) 2014.

contributions in this field and led the way in terms of clinical toxicology. It is now possible to identify the leading papers that have contributed to the development of this field of research. Scientific publications in lipid emulsion research increased during the last decade (i.e. 85.86% of documents were published in 2006–2015, and the yearly average growth in this field was 51 articles per year) in both absolute numbers and quality, especially in the USA and Europe. The rise of publications in lipid therapy was noticeable after 2006, which coincides with the first publication of successful use of lipid therapy in poisoning in human beings [46]. Since the initial successful report of the use of intravenous lipid emulsion in acute bupivacaine-induced cardiac arrest in 2006, it has been broadly applied for cardiac and neurological toxic medications including local anaesthetic agents, tricyclic antidepressants and non-dihydropyridine calcium channel blockers [36]. However, in the last decade, there was a bulk of emerging experimental evidence that lipid therapy can reverse some haemodynamically significant poisoning [8,37] with many fatal substances [52]. The most commonly reported substances include sedative/ hypnotics, analgesics, antidepressants, antipsychotics, stimulants, substances of abuse and cardiovascular drugs. Most of these substances have no specific antidote. Most existing data about the clinical efficacy of lipid emulsion in treating acute toxicity is available from case reports. Unfortunately, controlled randomized clinical trials of lipid emulsion in the treatment of acute toxicity are not found due to practical and ethical considerations, and the existing level of evidence in this field comes from animal studies, case reports and expert opinions, which is considered less than optimal [35].

It is worth noting that over 30% of the most published papers in the field of lipid emulsion originated from the USA. This demonstrates that the USA holds a significant position in scientific production on lipid emulsion research as an antidote for the treatment of acute poisoning. The USA has been a leader in health research for decades, including toxicology [20–23,53]. According to the Institute of Scientific Information (ISI), the USA achieves the highest ranking in all 20 scientific disciplines [54]. The USA, UK, France, Canada, New Zealand, Germany, Australia, China, Turkey and Japan produced approximately 75.6% of the total number of articles published in the field of lipid emulsion research.

The contribution of the developing world, such as Arab countries, to the research output in this field was rather disappointing. The better economic countries produced the higher the quantity and quality of its health publications [55,56]. As well as this finding, the total share of all health publications decreased for low-income countries [57,58]. There are several possible explanations for this finding. For instance, the lack of specialists in the field of clinical toxicology may have played a major role in the relatively low research output in this field [28]. One of the scientific challenges in toxicology in the Arab region is the limited availability of epidemiological data related to poisoning [28]. Another possible explanation for this finding may be the lack of adequate governmental financial

Table 3.
Top 10 most cited documents related to lipid emulsion in Scopus database [5–7,37,46–51].

SCR	Authors	Title	Year of publication	Source title	Cited by	IF
1st	Weinberg *et al.* [5]	Pre-treatment or resuscitation with a lipid infusion shifts the dose response to bupivacaine-induced asystole in rats	1998	*Anaesthesiology*	351	5.879
2nd	Rosenblatt *et al.* [46]	Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest	2006	*Anaesthesiology*	340	5.879
3rd	Weinberg *et al.* [6]	Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity	2003	*Regional Anaesthesia and Pain Medicine*	320	3.089
4th	Litz *et al.* [47]	Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion	2006	*Anaesthesia*	233	3.382
5th	Weinberg *et al.* [48]	Lipid infusion accelerates removal of bupivacaine and recovery from bupivacaine toxicity in the isolated rat heart	2006	*Regional Anaesthesia and Pain Medicine*	170	3.089
6th	Sirianni *et al.* [49]	Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine	2008	*Annals of Emergency Medicine*	154	4.676
7th	Foxall *et al.* [50]	Levobupivacaine-induced seizures and cardiovascular collapse treated with intralipid	2007	*Anaesthesia*	144	3.382
8th	Ludot *et al.* [51]	Successful resuscitation after ropivacaine- and lidocaine-induced ventricular arrhythmia after posterior lumbar plexus block in a child	2008	*Anaesthesia and Analgesia*	135	3.472
9th	Litz *et al.* [7]	Reversal of central nervous system and cardiac toxicity after local anaesthetic intoxication by lipid emulsion injection	2008	*Anaesthesia and Analgesia*	126	3.472
10th	Jamaty *et al.* [37]	Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies	2010	*Clinical Toxicology*	121	3.673

SCR, standard competition ranking; IF, impact factor.

support, which led to low scientific research output in the Arab world [28,59].

The quality of the research output in the field of lipid emulsion was considered based on the average citation rate per item. In our study, the average citation was 15.7 citations per item. In comparison with the findings of previous bibliometric studies, our findings showed that that the average citation rate for other toxicology fields was lower than the average citation of documents published in lipid emulsion [20,21,23].

It is commendable that the most cited articles originated from the USA, as well as one of the highest mean numbers of citations. This achievement has been demonstrated by many other citation analysis reports [60–65]. The most influential paper was cited 351 times and was published by Weinberg *et al.* [5] in 1998 in the USA. This article suggested a novel technique as a potential application for the infusion of lipid emulsion in treating cardiotoxicity resulting from anaesthetic intoxication (e.g. bupivacaine). The clinically relevant follow-up experiments and the subsequent experimental models which cited this article confirmed that lipid infusion still provided protection from the cardiac toxic effect of bupivacaine [35]. The second most frequently cited paper by Rosenblatt *et al.* [46] was published in 2006 as a case report in the USA. The authors reported the first successful use of lipid infusion to resuscitate a patient who had most likely sustained a local anaesthetic-induced cardiac arrest [46]. The next most cited paper was by Weinberg *et al.* [6] in 2003, and was published as an original article in the USA. They demonstrated that infusing a lipid emulsion during resuscitation from bupivacaine-induced cardiac toxicity significantly increased survival and improved haemodynamics, myocardial tissue oxygen pressure and myocardial pH in dogs [6]. This suggests that the USA is an incredibly productive country and also creates high-quality publications.

Table 4.
Top 10 highly productive institutions publishing lipid emulsion research in Scopus database between 1955 and 2015.

SCR[1]	Institution	Country	No. of documents (%)
1st	University of Illinois at Chicago	USA	26 (4.4)
2nd	Waikato Hospital	New Zealand	22 (3.7)
3rd	University of Illinois College of Medicine	USA	20 (3.4)
4th	Hutt Hospital	New Zealand	17 (2.9)
5th	VA Medical Center	USA	13 (2.2)
6th	Helsingin Yliopisto (University of Helsinki)	Finland	10 (2.0)
6th	Jesse Brown VA Medical Center	USA	10 (1.7)
8th	Regions Hospital	USA	8 (1.3)
8th	New York University School of Medicine	USA	8 (1.3)
8th	University of Alberta	Canada	8 (1.3)

SCR, standard competition ranking.
[1]Equal institutions have the same ranking number, and then, a gap is left in the ranking numbers.

The most interesting finding was that international collaboration in the current study was less than that found in previous bibliometric studies in different fields [20,41,66,67]. International research collaboration requires skills in problem identification and problem-solving activities to be shared [68]. International research collaboration enhances the quality of the research by increasing citation rates [69,70]. However, low incidence of poisonings requiring use of lipid emulsion therapy is probably the most important problem leading to the lack of high-level scientific evidence in this field [19,33,38]. There is an obvious need of international collaborations for the development of randomized clinical outcome trials to reach high-level scientific evidence in lipid emulsion for poisoning.

We must acknowledge that the bibliometric method has some potential limitations, as described in our original bibliometric studies [71–73]. We used the Scopus database to recognize the selected keywords in the field of lipid emulsion for inclusion in the study. Documents published in non-Scopus-cited journals were not included.

Conclusions

In summary, we evaluated the global research output in the field of lipid emulsion research as an antidote for the treatment of acute poisoning for 1955–2015. We found an increase in the number of publications in the field of lipid emulsion after 2006. The results of the current study demonstrated that the majority of publications in the field of lipid emulsion were published by high-income countries. Researchers from institutions in the USA led scientific production in lipid emulsion research. There is an obvious need to promote a deeper engagement through international collaborative research projects and funding mechanisms.

Competing Interests

The authors declared that they have no competing interests.

Acknowledgements

The authors would like to thank An-Najah National University for providing the opportunity to access the most recent information sources such as the Scopus database.

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