Drug Design, Development and Therapy

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REVIEW

High-Impact Clinical Studies That Fomented New Developments in Anesthesia: History of Achievements, 1966–2015

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Abstract: The aim of this work is to identify the most influential initial clinical studies that fomented important developments in anesthesiology over the past 50 years. Studies fomenting new development can be selected using vastly different approaches and, therefore, might provide diverse outcomes. In the present work, two basic aspects of study assessments – the stage of development (eg, generation of idea, preclinical studies, clinical trials) and the method of selection (eg, committee vote, various types of citation analysis, method of finding the invention disclosure) – were chosen according to the following model. The stage of development: the initial clinical studies demonstrating the basic advantage of an innovation for providing anesthesia. The method: a combination of two factors – the study priority in terms of the time of its publication and the degree of its acknowledgement in the form of citation impact; the time of study publication was regarded as a primary factor, but only if the study's citation count was =/>20. The initial high-impact studies were selected for 16 drug-related topics (ketamine, isoflurane, etomidate, propofol, midazolam in anesthesia, vecuronium, alfentanil, atracurium, sevoflurane, sufentanil, rocuronium, desflurane, ropivacaine, remifentanil, dexmedetomidine in anesthesia, and sugammadex), and 9 technique-related topics (ultrasound-guided peripheral nerve block, capnography in anesthesia, target-controlled intravenous anesthesia, pulse oximetry in anesthesia, total intravenous anesthesia, transesophageal echocardiography in anesthesia, combined spinal-epidural anesthesia, and bispectral index). Twenty-five studies were designated the first high-impact studies (one for each topic); 16 are drug-related and 9 are technique-related. Half of the first high-impact studies had a citation count of =/>100, (range: 100 to 555). The citation count of the other half of high-impact studies did not reach the 100-citation threshold (range: 41 to 97). If a selected first high-impact study had a citation count <100, a next-on-timeline, additional study with citation count =/>100 was also selected; (range: 100 to 344). The present results show that an initial high-impact clinical study on a new development in anesthesiology can be determined and that related citations usually vary from one hundred to five hundred.

Keywords: anesthetic techniques, citation impact, clinical trials, drugs, priority rules, scientometrics

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Introduction

In a previous study,[1] we analyzed important new developments in anesthesiology over the past 50 years. The topics for such developments were selected using an objective indicator – the degree to which the number of academic articles on a topic increased. More than 20 such topics were identified. The aim of this study was to

Received: 20 April 2021
Accepted: 21 May 2021
Published: 11 June 2021

determine for each of these topics the most influential initial clinical studies, also using an objective indicator – the number of citations generated by the study's publication.

In science, priority rule is the credit given to the person who first published a new finding or proposed a theory.[2,3] Determining priority of discovery is a two-step process that includes its disclosure and validation.[4] The validation reflects the scientific community's response to a disclosure centered on two questions: Is a new finding correct, and is it of sufficient interest to merit attention and further development? In practice, this acknowledgement usually comes in the form of citations in papers by other scientists, which can accumulate over time. Unlike disclosure (eg, publication), which is an event with a definite time stamp, validation can take a variable amount of time.[4]

The chain of accomplishments leading to any important new development has many links. Among the main ones are disclosure(s) of a new idea (eg, patents), definitive bench and/or animal studies, and human studies leading to the formal approval of a drug or technique for use in clinical practice. The aim of the current study is to assess only one of these links – initial clinical studies that prominently contributed to the acceptance of a new development by the scientific community. We sought to assess the contribution of initial clinical studies to the success of a new development by combining two factors: the time of the study publication and its acknowledgement by the scientific community in the form of total citation impact. For this, we identified initial studies that proved the effectiveness of a drug (or technique) in achieving a specific aim in anesthesia, and were the first to have an impressive citation impact.

Methods

On Topics of New Developments

The selection of the topics of new developments was based on the results of the previous study, in which the degree of increase in the number of academic articles on a topic was used for selection.[1] The main tool for selection was popularity index (PI),[5] the percentage of articles on the topic among all articles related to the PubMed (MeSH) term "Anesthesia" over the same 5-year period. A topic was selected if it had reached a PI =/> 0.5 during any 5-year period from 1966 to 2015, or the total number of articles on the topic reached at least 500 articles.[1] There were 27 such topics, 19 of them were drug-related (ketamine, isoflurane, enflurane, etomidate, propofol, midazolam in anesthesia, vecuronium, alfentanil, atracurium, sevoflurane, sufentanil, mivacurium, rocuronium, desflurane, ropivacaine, remifentanil, dexmedetomidine in anesthesia, levobupivacaine, and sugammadex) and 9 technique-related (ultrasound-guided peripheral nerve block, capnography in anesthesia, target-controlled intravenous anesthesia, pulse oximetry in anesthesia, total intravenous anesthesia, transesophageal echocardiography in anesthesia, combined spinal-epidural anesthesia, bispectral index, and transversus abdominis plane block). In the present study, we excluded from the list of drugs three agents that were discontinued in the USA in 2020 – enflurane, mivacurium, and levobupivacaine; the list of technique-related topics was not modified. Basic search details on these topics are presented in Table 1.

Requirements for Selection of Initial High-Impact Studies

General Requirements

The selection of initial high-impact studies was based on the following general requirements: 1) the principal aim of the study should be the assessment of the effectiveness of a new agent (or technique) in achieving a specific aim in anesthesia; 2) the study should be published as an original research article; 3) the study should be one of the initial clinical studies on a topic; 4) the study should have an impressive citation impact (the Thomson Reuters Web of Science Database),[6] preferably more than 100, but not fewer than 20 citations, most importantly, it should be published before other clinical studies on the topic with citation records =/> 20. If the study had a citation record =/> 20, but not =/> 100, an additional study with =/> 100 citations was also selected, on condition that it was published the next on the timeline after the first study. As a result, there were two types of initial studies with =/> 100 citations: the first high-impact studies with =/> 100 citations and the additional high-impact studies with =/> 100 citations. The choice of the number of citations thresholds (20 and 100) was a voluntary one.

Specific Requirements

Specific requirements for the selection of studies with 20-citation threshold: If several studies with =/> 20 citations were published almost simultaneously (within six-month period), all of them were identified, unless they had <30% of the number of citations of the study with the highest citation rate.

Table 1 Search Details on Initial High-Impact Clinical Studies

(A) Drugs						
#	Topic	Patent		Search Timespan	Search Terms	Additional MeSH Headings[b]
		Year[a]	Inventors			
1	Ketamine	1963	Stevens CL	1963–1972	Ketamine, CI-581, Ketalar	Anesthesia, Humans
2	Isoflurane	1969	Terrell RC	1969–1976	Isoflurance, Forane	Anesthesia, Humans
3	Etomidate	1964	Fred GE, Eijcken CAMV	1964–1976	Etomidate, R26490	Anesthesia, Humans
4	Propofol	1974	Glen JB, James R	1976–1984	Propfol, ICI 35868, Diprivan	Anesthesia, Humans
5	Midazolam in anesthesia	1973	Fryer RI, Walser A	1973–1981	Midazolam, RO 21–3981	Anesthesia, Humans
6	Vecuronium	1974	Hewett CL, Savage DS	1974–1982	Vecuronium, ORG NC45	Anesthesia, Humans
7	Alfentanil	1978	Janssens FPB	1978–1986	Alfentanil, R-39209	Anesthesia, Humans
8	Atracurium	1975	Stenlake JB, Waigh RO, Dewar CH	1975–1983	Atracurium, 33A74	Anesthesia, Humans
9	Sevoflurane	1969	Terrell RC	1969–1987	Sevoflurane	Anesthesia, Humans
10	Sufentanil	1976	Janssen PAJ, Van Daele GHP	1976–1984	Sufentanil, R30730	Anesthesia, Humans
11	Rocuronium	1990	Sleigh T, Carlye IC, Muir AW	1990–1996	Rocuronium, ORG9426	Anesthesia, Humans
12	Desflurane	1987	Terrell RC	1987–1992	Desflurane, I-653	Anesthesia, Humans
13	Ropivacaine	1986	Sandberg RV	1986–1992	Ropivacaine	Anesthesia, Humans
14	Remifentanil	1989	Feldman PL, James MK, Brackeen MR, et al.	1989–1998	Remifentanil	Anesthesia, Humans
15	Dexmedetomidine in anesthesia	1988	Karjalainen AJ, Virtanen RE, Savolainen EJ	1988–2003	Dexmedotomidine	Anesthesia, Humans
16	Sugammadex	2000	Zhang M, Palin R, Bennett J	2000–2008	Sugammadex, ORG 25969	Anesthesia, Humans

(*Continued*)

Table 1 (Continued).

(B) Techniques						
#	Topic	Patent		Search Timespan	Search Terms	Additional MeSH Headings[b]
		Year[a]	Inventors			
1	Ultrasound-guided peripheral nerve block	-	-	1977–1995	"Ultrasound-guided AND Nerve Block NOT Biopsy"	Anesthesia, Humans
2	Capnography in anesthesia	-	-	1982–1989	"Capnography OR Capnometry OR End-tidal PCO2"	Anesthesia, Humans
3	Target-controlled intravenous anesthesia	-	-	1982–1993	"Target-controlled intravenous anesthesia OR Target-controlled infusion"	Anesthesia, Humans
4	Pulse oximetry in anesthesia	1979	Aoyagi T, Kobayashi N, Sasaki T	1982–1989	"Pulse oximetry"	Anesthesia, Humans
5	Total intravenous anesthesia	-	-	1985–1997	"Total intravenous anesthesia OR TIVA"	Anesthesia, Humans
6	Transesophageal echocardiography in anesthesia	-	-	1986–1996	"Transesophageal echocardiography OR TEE"	Anesthesia, Humans
7	Combined spinal-epidural anesthesia	-	-	1982–1989	"Combined spinal- epidural OR Combined subarachnoid and epidural"	Anesthesia, Humans
8	Bispectral index			1994–2000	"Bispectral index OR BIS"	Anesthesia, Humans
9	Transversus abdominis plane block			2005–2008	"Transversus abdominis plane block"	Anesthesia, Humans

Notes: [a]Year of worldwide patent application (Google Patent); [b]MeSH (Medical Subject Headings) vocabulary of Medline database.

Specific requirements for the selection of additional studies with 100-citation threshold: 1) If the =/> 100 citations study is an additional one, its date of publication should be closest to that of the first study with <100 citations (but >20 citations). 2) If several studies with the =/>100 citation count were published during the same six-month period, all were listed according to their publication dates. Any of these studies with fewer than 30% of the citations of the first study were excluded.

Results

Table 2 presents data on studies according to the number of citations they elicited as well as their publication dates (year and month), which are the principal criteria for the assessment of their priority. The table indicates the first authors of the articles, all other authors (along with the article titles, journal names, and other publication details). The review's list of selected studies as systemized in Table 2 can be viewed in Supplement. In Table 2 studies are divided into two categories: those which crossed only =/> 20 citation-threshold and those which crossed a higher threshold, =/> 100 citations. The selected studies were prioritized based on publication date, but only if their citation count was =/> 20. Subject to a number of specifications (presented in the Methods), one study for each topic was designated as the first high-impact study. If the first high-impact study did not reach the 100 citation-threshold, the study next to it on the timeline was also selected; it was designated as the additional high-impact study – published at a later date, but having a higher citation count. As a result, there were two types of initial studies with =/>100 citations: the first studies with =/> 100 citations and additional studies with =/>100 citations; both of them are presented in Table 2. They are listed separately in Table 3.

Table 2 Initial High-Impact Clinical Studies in Major Anesthesia Developments Since 1965

(A) Drugs							
#	Topic	Studies According to Number of Citations					
		≥20 Threshold[a]			≥100 Threshold		
		First Author and Journal	Time of Publication	Number of Citations	First Author and Journal	Time of Publication	Number of Citations
1	Ketamine	–	–	–	Domino EF[7] *Clin Pharmacol Ther*	1965 (May - Jun)	555
2	Isoflurane	Dobkin AB[8] *Can Anaeth Soc J*	1971 (May)	43	Stevens WC[9] *Anesthesiology*	1971 (Jul)	344
3	Etomidate	Doenicke A[10] *Anaesthetist*	1973 (Aug)	72	Holdcroft A[11] *Br J Anaesth*	1976 (Mar)	100
4	Propofol	-	-	-	Kay B[12] *Acta Anaesth Belg*	1977 (Feb)	122
5	Midazolam in anesthesia	-	-	-	Conner JT[13] *Anesth Analg*	1978 (Jan - Feb)	106
					Reves JG[14] *Can Anaesth Soc J*	1978 (May)	118
					Fragen RJ[15] *Anesthesiology*	1978 (Jul)	128
6	Vecuronium	-	-	-	Agoston S1[16] *Br J Anaesth*	1980 (Jun)	125
					Krieg N[17] *Br J Anaesth*	1980 (Aug)	95
7	Alfentanil	Kay B[18] *Anaesthesia*	1980 (Dec)	41	Ausems ME[19] *Anesthesiology*	1986 (Oct)	210
8	Atracurium	-	-	-	Payne JP[20] *Br J Anaesth*	1981 (Jan)	212
9	Sevoflurane	-	-	-	Holaday DA[21] *Anesthesiology*	1981 (Feb)	194
					Katoh T[22] *Anesthesiology*	1987 (Mar)	229
10	Sufentanil	Bovill JG[23] *Br J Anaesth*	1982 (Jan)	48	de Lange S[24] *Anesthesiology*	1982 (Feb)	143
11	Rocuronium	-	-	-	Wierda JM[25] *Br J Anaesth*	1990 (Apr)	132
12	Desflurane	Jones RM[26] *Anesth Analg*	1990 (Jan)	76	Rampil IJ[27] *Anesthesiology*	1991 (Mar)	169

(*Continued*)

Table 2 (Continued).

13	Ropivacaine	Katz JA[28] *Anesth Analg*	1990 (Jan)	70	Brockway MS[31] *Br J Anaesth*	1991 (Jan)	146
		Concepcion M[29] *Anesth Analg*	1990 (Jan)	63			
		Brown DL[30] *Anesthesiology*	1990 (Apr)	74			
14	Remifentanil	Dershwitz M[32] *Anesth Analg*	1995 (Sep)	97	Hogue CW Jr[33] *Anesth Analg*	1996 (Aug)	161
					Lang E[34] *Anesthesiology*	1996 (Oct)	165
15	Dexmedetomidine in anesthesia	Aantaa RE[35] *Anesth Analg*	1990 (Apr)	67	Aantaa R[36] *Anesthesiology*	1990 (Aug)	175
16	Sugammadex	-	-	-	Gijsenbergh F[37] *Anesthesiology*	2005 (Oct)	179
					Shields M[38] *Br J Anaesth*	2006 (Jan)	118
(B) Techniques							
#	**Topic**	**Studies According to Number of Citations**					
		≥20 Threshold[a]			**≥100 Threshold**		
		First Author and Journal	**Time of Publication**	**Number of Citations**	**First Author and Journal**	**Time of Publication**	**Number of Citations**
1	Ultrasound-guided peripheral nerve block	La Grange P[39] *Br J Anaesth*	1978 (Sep)	65	Kapral S[40] *Anesth Analg*	1994 (Mar)	219
2	Capnography in anesthesia	-		-	Linko K[41] *Acta Anaesth Scand*	1983 (Jun)	102
3	Target-controlled intravenous anesthesia	Schuttler J[42] *Anaesthesia*		65	Schwilden H[43] *Anesthesiology*	1987 (Sen)	226
4	Pulse oximetry in anesthesia	-	-	-	Yelderman M[44] *Anesthesiology*	1983 (Oct)	364
5	Total intravenous anesthesia	de Grood PM[45] *Postgrad Med J*	1985 (Jan)	46	Hogue CW Jr[33] *Anesth Analg*	1996 (Aug)	162
6	Transesophageal echocardiography in	-	-	-	Roizen MF[46] *J Vasc Surg*	1984 (Mar)	140
7	Combined spinal-epidural anesthesia	-	-	-	Rawal N[47] *Acta Anaesth Scand*	1988 (Jan)	125

(*Continued*)

Table 2 (Continued).

8	Bispectral index	Kearse LA[48] *Electroenceph Clin Neurophysiol*	1994 (Mar)	50	Kearse LA[49] *Anesthesiology*	1994 (Dec)	133
					Vernon JM[50] *Anesth Analg*	1995 (Apr)	163
9	Transversus abdominis plane block	-	-	-	McDonnell JG[51] *Anesth Analg*	2007 (Jan)	421

Notes: [a]High-impact study crossing threshold of ≥20 citations, but not threshold of ≥100 citations; The numeral at the name of first author represents the reference number in the list of references.

Overall, 25 studies were designated as first high-impact studies, 16 of which are drug-related and 9 technique-related. Only half of the first high-impact studies had a citation count of =/>100: 8 of 16 with drug-related topics, from 106 to 555 citations; and 4 of 9 with technique-related topics, from 102 to 421 citations. The other half of the first high-impact studies did not reach the 100-citation threshold: for drug-related topics their counts were from 41 to 97, and for technique-related topics – 46 to 65. There were no citation counts below 40 with any topic, although citation rates from 20 to 40 were searched for. Given the principles for selection, all additional high-impact studies had =/>100 citations (Table 3, right column): with eight drug-related topics the citations count varied from 100 to 344, and with four technique-related topics – from 133 to 219.

The selection of the first high-impact study (or the additional high-impact study) was often made more difficult by the presence of several studies with very close dates of publication and similar citation counts. The greatest difficulties in this respect were with five drug-related topics: midazolam, vecuronium, sevoflurane, ropivacaine, and sugammadex. This can be seen when dates of publication and citation counts of several similar high-impact studies (Table 2) are compared with those of a single study presented as the final choice (Table 3). For example, there were three studies on the use of midazolam for anesthesia published in 1978: Conner[13] in January–February, Reves[14] in May, and Fragen[15] in July; the citation counts for all three studies varied only from 106 to 128. The choice of Conner's study (Table 3) was based on several months earlier publication. Another example is the three studies on ropivacaine published in 1990: Katz[28] in January, Concepcion[29] in January, and Brown[30] in April. In this case, two studies (Katz and Concepcion) were published in the same issue of Anesthesia & Analgesia and had similar citation counts – 70 and 63, respectively (Table 2). Both studies are placed in Table 3 as the first high-impact study, as an exception to the rule of one study per topic.

Discussions

In this review, we identified the initial high-impact clinical studies which fomented new developments in anesthesiology over the past 50 years. These studies were assessed by combining two factors: the study's publication date and the degree of its acknowledgement by the scientific community in the form of citations. As a result, twenty-five studies were designated the first high-impact studies (one for each topic); 16 are drug-related and 9 are technique-related. Half of the first high-impact studies had a citation count of =/>100, (range: 100 to 555). The citation count of the other half of high-impact studies did not reach the 100-citation threshold (range: 41 to 97). If a selected first high-impact study had a citation count <100, a next-on-timeline, additional study with citation count =/>100 was also selected (range: 100 to 344).

These studies represent 25 topics of the most meaningful developments in anesthesiology. What is a meaningful development? According to Helmer,[52] one of the most important conditions for meaningful research is a practically useful impact on society. In this review, due to the retrospective view of developments whose usefulness was confirmed during many decades of clinical practice, research studies with impact on these developments were historically shown to be practically useful. They include the following topics which are well known to any anesthesiologist. Sixteen drug-related topics: ketamine, isoflurane, etomidate, propofol, midazolam in anesthesia, vecuronium, alfentanil, atracurium,

Table 3 Number of Citations Generated by Initial High-Impact Clinical Studies

(A) Drugs					
#	**Topic**	**First Study**[a]		**Additional Study**[b]	
		Citation Impact	**First Author**	**Citation Impact**	**First Author**
1	Ketamine	555	Domino EF[7]	–	–
2	Isoflurane	43	Dobkin AB[8]	344	Stevens WC[9]
3	Etomidate	72	Doenicke A[10]	100	Holdcroft A[11]
4	Propofol	122	Kay B[12]	–	–
5	Midazolam in anesthesia	106	Conner JT[13]	–	–
6	Vecuronium	125	Agoston S[16]	–	–
7	Alfentanil	41	Kay B[18]	210	Ausems ME[19]
8	Atracurium	212	Payne JP[20]	–	–
9	Sevoflurane	194	Holaday DA[21]	–	–
10	Sufentanil	48	Bovill JG[23]	144	DeLange S[24]
11	Rocuronium	132	Wierda JM[25]	–	–
12	Desflurane	76	Jones RM[26]	169	Rampil IJ[27]
13	Ropivacaine	70	Katz JA[28]	146	Brockway MC[31]
		63	Conceptcion[29]		
14	Remifentanil	97	Dershwitz M[32]	161	Hogue GW Jr[33]
15	Dexmedetomidi ne in anesthesia	67	Aantaa R[35]	175	Aantaa R[36]
16	Sugammadex	179	GijsenberghF[37]	–	–
(B) Techniques					
#	**Topic**	**Initial Study**[a]		**Additional Study**[b]	
		Citation Impact	**First Author**	**Citation Impact**	**First Author**
1	Ultrasound-guided peripheral nerve block	65	La Grange P[39]	219	Kapral S[40]
2	Capnography in anesthesia	201	Linko K[41]	-	-
3	Target-controlled intravenous anesthesia	65	Schuttler J[42]	226	Schwilden H[43]
4	Pulse oximetry in anesthesia	364	Yelderman M[44]	-	-
5	Total intravenous anesthesia	46	de Grood PM[45]	162	Hogue CW Jr[33]
6	Transesophageal echocardiography in anesthesia	140	Roizen MF[46]	-	-
7	Combined spinal- epidural anesthesia	125	Rawal N[47]	-	-
8	Bispectral index	50	Kearse LA[48]	133	Kearse LA[49]
9	Transversus abdominis plane block	421	McDonnell JG[51]	-	

Notes: [a]First study with citation impact ≥20; [b]If the first study had <100 citation, the next-on-timeline study with ≥100 citations was added.

sevoflurane, sufentanil, rocuronium, desflurane, ropivacaine, remifentanil, dexmedetomidine in anesthesia, and sugammadex; and also nine technique-related topics: ultrasound-guided peripheral nerve block, capnography in anesthesia, target-controlled intravenous anesthesia, pulse oximetry in anesthesia, total intravenous anesthesia, transesophageal echocardiography in anesthesia, combined spinal-epidural anesthesia, and bispectral index.

It is important to underline that all selected studies had two specific features. First, only original research articles, in which the principle goal was the assessment of possible use of a new agent or technique for achieving a specific aim in anesthesia, were selected. Studies beyond the initial question of the basic advantage of a new drug (or technique) for anesthesia, such as drug's formulation, the general characteristic of drug's pharmacokinetics, or possible additional clinical indications, were not selected as the initial high-impact studies.

Second, only initial clinical studies were selected. Their impact on the opinion of the scientific community was sufficient to convince it that a new agent or technique is of interest for further development, indicating that the previous chain of events, from conceiving an idea (eg, patent) to bench or/and animal experiments, and finally to clinical trial, had real promise. The high citation impact of the initial clinical study elevates a new agent, following multiple study-steps on various aspects of the agent's action, to its destination – formal approval for use in clinical practice. In the long life of an introduced drug or technique, significant new research findings may change the drug's role in clinical practice. This assessment concentrated only on initial clinical studies that gave birth to new developments.

Among limitations of this review is, described in the methods, voluntary choice of the number of citations thresholds for selecting the studies. The other limitation is associated with the preselected aspects of the review, which requires the following explanation. The presented analysis of the studies has two aspects: 1) Which stage of development to analyze, and 2) What method to use. With the first aspect, each new development has a number of stages, such as the generation of a novel idea, its disclosure in a patent, definitive bench or/and animal studies, initial clinical studies, and advanced clinical studies leading to formal approval for general use in clinical practice. The aim of present assessment was to analyze only initial clinical studies. The second aspect, related to the methods of comparative assessment of the studies on a new development, could be based on a list established by academic leaders or through committee vote;[53] another more objective one is based on various methods derived from raw citation data;[54] the most important factor in discovery assessment is associated with the date of disclosure.[3] In the present assessment, a combination of two factors was used: the study's priority in terms of the time of its publication and the degree of its acknowledgement by the academic community in the form of citations. With different approaches to these two aspects of analysis – what stage to analyze and what method to apply for the study selection – various outcomes are possible. This may be regarded as a potential limitation of the current review. For example, our approach, based on initial clinical studies, is not directed toward the most important element of any new development – the generation of a new idea including its disclosure (eg, patent). At the same time, it was centered on the most critical consideration in the development of a new idea – is it clinically useful? Thus, with different approaches the importance of different studies could be assessed quite differently; therefore, our results should be regarded only as an initial attempt in the selection of high-impact studies that fomented new developments in anesthesia.

In conclusion, the present results show that an initial high-impact clinical study on a new development in anesthesiology can be determined and that related citations usually vary from one hundred to five hundred. The review's List of Selected Studies. These initial clinical studies fomented the most important development in anesthesiology over the past 50 years.

Disclosure

The author reports no conflicts of interest in this work.

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