

REVIEW

MORTALITY IN ANESTHESIA: A SYSTEMATIC REVIEW

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doi: 10.1590/S1807-59322009001000011

Braz LG, Braz DG, Cruz DS, Fernandes LA, Módolo NSP, Braz JRC. Mortality in anesthesia: a systematic review. Clinics. 2009;64(10):999-1006.

This systematic review of the Brazilian and worldwide literature aims to evaluate the incidence and causes of perioperative and anesthesia-related mortality. Studies were identified by searching the Medline and Scielo databases, followed by a manual search for relevant articles. Our review includes studies published between 1954 and 2007. Each publication was reviewed to identify author(s), study period, data source, perioperative mortality rates, and anesthesia-related mortality rates. Thirty-three trials were assessed. Brazilian and worldwide studies demonstrated a similar decline in anesthesia-related mortality rates, which amounted to fewer than 1 death per 10,000 anesthetics in the past two decades. Perioperative mortality rates also decreased during this period, with fewer than 20 deaths per 10,000 anesthetics in developed countries. Brazilian studies showed higher perioperative mortality rates, from 19 to 51 deaths per 10,000 anesthetics. The majority of perioperative deaths occurred in neonates, children under one year, elderly patients, males, patients of ASA III physical status or poorer, emergency surgeries, during general anesthesia, and cardiac surgery followed by thoracic, vascular, gastroenterologic, pediatric and orthopedic surgeries. The main causes of anesthesia-related mortality were problems with airway management and cardiocirculatory events related to anesthesia and drug administration. Our systematic review of the literature shows that perioperative mortality rates are higher in Brazil than in developed countries, while anesthesia-related mortality rates are similar in Brazil and in developed countries. Most cases of anesthesia-related mortality are associated with cardiocirculatory and airway events. These data may be useful in developing strategies to prevent anesthesia-related deaths.

KEYWORDS: Anesthesia; Cardiac Arrest; Mortality, Perioperative; Review.

INTRODUCTION

Anesthesia has the potential to induce physiological changes that may lead to morbidity and mortality. As a result, it is commonly regarded as a high-risk activity. A number of investigators, however, have reported that anesthesia-related mortality rates have declined over the past two decades. This decrease has been attributed to a variety of safety improvements including improved monitoring techniques, the development and widespread adoption of

practice guidelines, and other systematic approaches to error reduction.^{1,2}

Nonetheless, trends in the frequency of anesthesia-related mortality remain controversial. According to a recent review,³ the literature reports a wide range of perioperative mortality rates, which is probably due to variable methodologies and differences in operational definitions and reporting sources, as well as a lack of appropriate risk stratification. Numerous studies have examined perioperative mortality.³⁻³¹ In these reports, the definitions for deaths in which anesthesia was the primary or a contributing cause³⁻³⁵ varied widely, as did the time windows for the considered perioperative period. The perioperative period has been defined as intraoperative only,^{12,14,16,24,33} intraoperative and recovery from anesthesia,^{24,29,31} the first 12 postoperative hours,³⁴ the first 24 postoperative hours,^{5,7,8,11,13,18,20,22,26,28,30,32,33} two

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Received for publication on April 28, 2009

Accepted for publication on July 03, 2009

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or three postoperative days,^{3,9,10,17,35} or seven postoperative days.^{6,19,21,23,25} Furthermore, mortality incidence may depend on the surgical population. Several studies examined all types of surgery,^{3-5,7-13,15-32,35} while others excluded surgeries in ASA V patients,³⁴ cardiac surgeries^{14,24,33} or obstetric surgeries.⁶ These wide variations based on methodological differences as reported in the literature make it impossible to detect trends in anesthesia safety.³

Large-scale and national studies of anesthesia-related mortality have been performed in some countries to confirm whether the mortality rate has indeed decreased.^{11,17,20,21,23,25,26,35} In Brazil, reliable data on anesthesia-related mortality have been collected,²⁷⁻³¹ but no nationwide study has been undertaken.

The purpose of our study was to perform a systematic review of the Brazilian and worldwide literature in order to evaluate the incidence and causes of perioperative and anesthesia-related mortality.

METHODS

The Medline (via PubMed) and Scielo databases were searched using the subject keywords “mortality, cardiac arrest and anesthesia”. We also used the “related articles” function on PubMed and Scielo with the references of the studies. Publications were included in our review if their titles or abstracts were available in English or Portuguese and suggested a perioperative mortality rate related to anesthetic management in a general patient population over a specific period of time based on original data from at least 25,000 anesthetics. The review was completed in July 2008. Publications were excluded if the anesthetic management was limited to a particular technique or the patient population was limited to a particular procedure, associated disease state, or age group. Other studies on anesthesia mortality that offered additional relevant information were also examined. Mortality-triggering factors were assigned to one of three groups: (i) surgery-related; (ii) related to patient disease or condition; or (iii) anesthesia-related when anesthesia was the major contributor or represented an additional factor associated with patient disease condition or surgical factor.

Each publication was reviewed in order to identify the author(s), study period, data source, perioperative mortality rate (including all death-triggering factors), and anesthesia-related mortality rate.

RESULTS

Database queries identified 33 publications reporting anesthesia-related mortality data, 28 from international

investigators (Tables 1 and 2) and 5 publications by Brazilian investigators (Table 3).

Comparison of the literature data reported by investigators from different countries between 1954 and 1989 with those obtained from 1990 to 2006 showed that anesthesia-related mortality rates decreased from 0.30 – 7.91 per 10,000 anesthetics⁴⁻¹³ (Table 1) to 0.10 – 5.70 per 10,000 anesthetics^{3,14-26,32-35} (Table 3). However, the highest anesthesia-related mortality rates were observed between 1990 and 2006 (3.3 to 5.7 per 10,000 anesthetics) and reported in studies performed in developing countries^{18,26} (Table 2).

In Brazil, reported anesthesia-related mortality rates also declined from 2.28 per 10,000 anesthetics in 1986²⁷ to 0.12 – 1.12 per 10,000 anesthetics between 1998 and 2006²⁸⁻³¹ (Table 3).

Comparison of the literature reported by worldwide investigators from 1954 to 1989 with papers published between 1990 and 2006 demonstrated that perioperative mortality rates declined from 2.4 – 188.9 per 10,000 anesthetics⁴⁻¹³ (Table 1) to 1.41 – 28.2 per 10,000 anesthetics^{3,14-23,25,26} (Table 2). Once more, the highest anesthesia-related mortality rates for the 1990-2006 period (20.14 to 28.2 per 10,000 anesthetics) were reported by investigators from developing countries^{15,18,26} (Table 2). The studies conducted in Brazil between 1986 and 2006 also revealed increased perioperative mortality rates varying from 19.1 to 51.0 per 10,000 anesthetics²⁷⁻³¹ (Table 3).

In both Brazilian^{28,30,31} and worldwide^{3,9,15,17,20-22,26} studies, the patient/disease condition represented the major perioperative mortality-triggering factor, followed by surgery and anesthesia. The incidence of mortality caused by surgical factors declined significantly during the last few decades.¹⁷

Cardiovascular effects caused by the administration of anesthetic drugs and inadequate blood management during hemorrhage and anemia have been the major contributing factors to anesthesia-related mortality during the past twenty years, followed by airway management failure.^{3,20,24,31,35-37}

Of the factors associated with the patient condition/disease or surgery, both Brazilian^{29,31} and worldwide^{22,26} studies have pointed to trauma as the major cause of perioperative mortality, followed by end-stage liver disease and liver transplantation-related complications, complications associated with cardiac surgery, and exsanguinating hemorrhage at operation associated with the primary disease.

In newborns and children under one year^{11,14,21-23,30} as well as in the elderly, mortality rates were higher than in young adults.^{11,12,17,21-23,28,35}

Poorer American Society of Anesthesiologists physical status (ASA III to V)^{11,14,29,31,34,35} and emergency

Table 1 - Mortality incidence in patients undergoing anesthesia according to studies performed in different countries between 1954 and 1989

Investigator and Year of Publication	Time Period and Data Source	Study Population and Time of Death	Mortality Incidence per 10,000 anesthetics	
			Perioperative	Anesthesia-Related
Beecher & Todd (1954) ⁴	1948 – 1952 Group of 10 hospitals USA	599,548 anesthetics Hospital death	133.05	6.40
Memery (1965) ⁵	1955 – 1964 Private hospital USA	69,291 anesthetics Deaths within 24h	25.84	3.18
Marx et al. (1973) ⁶	1965 – 1969 Teaching hospital USA	34,145 anesthetics Deaths within 7 days Excluded: Obstetric patients	188.90	7.91
Bodlander (1975) ⁷	1963 – 1972 Teaching hospital Australia	211,130 anesthetics Deaths within 24h or failure to regain consciousness	19.32	5.87
Harrison (1978) ⁸	1967 – 1976 Teaching hospital South Africa	240,483 anesthetics Deaths within 24h	102.04	2.20
Hovi-Viander (1980) ⁹	1975 Group of 100 hospitals Finland	338,934 anesthetics Deaths within 3 days	18.48	1.98
Turnbull et al. (1980) ¹⁰	1973 – 1977 Teaching hospital Canada	195,232 anesthetics Deaths within 48h	22.0	1.28
Tiret et al. (1986) ¹¹	1978 – 1982 Group of 460 hospitals France	198,103 anesthetics Deaths within 24h	18.28	3.45
Olsson & Hallen (1988) ¹²	1967 – 1984 Teaching hospital Sweden	250,543 anesthetics Deaths in the OR	2.40	0.30
Pitt-Miller (1989) ¹³	1976 – 1987 General hospital India	129,107 anesthetics Deaths within 24h	14.41	6.58

OR = Operating Room

surgery^{11,12,17,21,22,27,29,31} have been considered risk factors for perioperative mortality. In addition, higher perioperative mortality incidence has been reported in males.^{22,28,30,31,35}

With regard to anesthesia type, perioperative mortality has been reported to be higher in patients undergoing general anesthesia as compared to those undergoing neuraxial anesthesia.^{20,27,30,31,35} Mortality incidence during surgeries carried out under plexus block has been reported as practically zero.^{29,31,34}

A higher number of intraoperative deaths have occurred during cardiac surgeries, followed by thoracic, vascular, gastroenterologic, pediatric, and orthopedic surgeries.^{20,22,28,30,31,35}

DISCUSSION

Substantial differences in methodology make it very difficult to compare anesthesia-related mortality

rates among studies.³ Despite the difficulties, studies undertaken in different countries (Tables 1 and 2) suggest that anesthesia-related mortality rates are lower today than they were 20 years ago. The pioneering study of Beecher and Todd (1954),⁴ which covered the period between 1948 and 1952, reported an anesthesia-related mortality rate of 6.40 per 10,000 anesthetics. Over the past two decades, most of the published studies have reported anesthesia-related mortality rates ranging from 0.5 to 1.0 per 10,000 anesthetics^{3,14,22,34,35} or even lower,^{15-17,19,23-25,33} which is at least a ten-fold improvement. In support of this assertion, the authors of a nationwide survey performed in France in 1999³⁵ reported that, in comparison with data obtained in a previous nationwide study (1978-1982), anesthesia-related mortality in France seemed to be reduced ten-fold in that country.

Some Brazilian studies conducted at the same kinds of institutions point to the same trend. According to these

Table 2 - Mortality incidence in patients receiving anesthesia according to studies performed in different countries between 1990 and 2006

Investigator and Year of Publication	Time Period and Data Source	Study Population and Time of Death	Mortality Incidence per 10,000 anesthetics	
			Perioperative	Anesthesia-Related
Chopra et al. (1990) ¹⁴	1978 – 1987 Teaching hospital Holland	113,074 anesthetics Deaths in the OR Excluded: cardiac surgery	1.41	0.53
Harrison (1990) ³²	1956 – 1987 Teaching hospital South Africa	750,00 anesthetics Deaths within 24h	-	1.90
Wu et al. (1991) ¹⁵	1988 – 1989 General hospital China	52,128 anesthetics Deaths within 7 days	20.14	0.40
Tan & Delilkan (1993) ¹⁶	1980 – 1992 Teaching hospital Malaysia	155,000 anesthetics Deaths in the OR	8.06	0.39
Kubota et al. (1994) ³³	1962 – 1992 Teaching hospital Japan	85,708 anesthetics Deaths in the OR Excluded: cardiac surgery	-	0.12
Tikkanen & Hovi-Viander (1995) ¹⁷	1986 Group of hospitals Finland	325,585 anesthetics Deaths within 3 days	17.61	0.15
Mckenzie (1996) ¹⁸	1992 Teaching hospitals Zimbabwe	34,533 anesthetics Deaths within 24h or failure to regain consciousness	25.80	3.30
Wu et al. (1997) ¹⁹	1993 – 1996 General hospital China	104,600 anesthetics Deaths within 7 days or failure to regain consciousness	3.25	0.29
Arbous et al. (2001) ²⁰	1995 – 1997 Group of hospitals Holland	869,483 anesthetics Deaths within 24 h	8.80	1.40
Biboulet et al. (2001) ³⁴	1989 – 1995 Teaching hospital France	101,769 anesthetics Death within 12 h Excluded: ASA V patients	-	0.60
Kawashima et al. (2002) ²¹	1999 Group of hospitals Japan	793,847 anesthetics Deaths within 7 days	3.44	0.13
Lagasse (2002) ³	1992 – 1999 Teaching hospitals USA	184,472 anesthetics Deaths within 2 days	18.90	0.77
Newland et al. (2002) ²²	1989 – 1999 Teaching hospital USA	72,959 anesthetics Deaths within 24h	14.11	0.95
Kawashima et al. (2003) ²³	1994 – 1998 Group of hospitals Japan	2,363,038 anesthetics Deaths within 7 days	4.05	0.21
Sprung et al. (2003) ²⁴	1990-2000 General hospital USA	518,294 anesthetics Deaths in OR or PARR Excluded: cardiac surgery	-	0.10
Irita et al. (2004) ²⁵	1999-2002 Group of hospitals Japan	3,855,384 anesthetics Deaths within 7 days	6.85	0.10
Charuluxananan et al. (2005) ²⁶	2003-2004 Group of hospitals Thailand	163,403 anesthetics Deaths within 24 h	28.20	5.70
Lienhart et al. (2006) ³⁵	1999 Group of hospitals France	7,773,655 anesthetics Deaths within 3 days	-	0.54

OR = Operating room; PARR =Post-anesthesia recovery room.

Table 3 - Mortality incidence in patients receiving anesthesia according to Brazilian publications between 1980 and 2000

Investigator and Year of Publication	Time Period and Data Source	Study Population and Time of Death	Mortality Incidence per 10,000 anesthetics	
			Perioperative	Anesthesia-Related
Ruiz Neto & Amaral (1986) ²⁷	1982 – 1984 Teaching hospital São Paulo (SP)	51,422 anesthetics Deaths in the OR	19	2.28
Cicarelli et al. (1998) ²⁸	1995 Teaching hospital São Paulo (SP)	25,926 anesthetics Deaths within 24 h	49.78	0.77
Braz et al. (1999) ²⁹	1988 – 1995 Teaching hospital Botucatu (SP)	58,553 anesthetics Deaths in the OR or PARR	21.17	0.85
Chan & Auler Jr (2002) ³⁰	1998 – 1999 Teaching hospital São Paulo (SP)	82,641 anesthetics Deaths within 24 h	51	0.12
Braz et al. (2006) ³¹	1996 – 2004 Teaching hospital Botucatu (SP)	53,718 anesthetics Deaths in the OR or PARR	21.97	1.12

OR = Operating room; PARR =Post-anesthesia recovery room.

studies, anesthesia-related mortality rates decreased from 2.28 per 10,000 anesthetics in the period of 1982-1984²⁷ to 0.77 per 10,000 in 1995,²⁸ and to 0.12 per 10,000 in 1998-1999.³⁰ Other Brazilian studies in another institution reported lower and stable anesthesia-related mortality rates ranging from 0.85 per 10,000 anesthetics in 1988-1995²⁹ to 1.12 per 10,000 anesthetics in 1996-2004.³¹

Considering the differences in patient risk and complexity of surgery five decades ago, it may be easy to conclude that anesthesia safety has dramatically increased over the past two decades. However, surveys of anesthesia-related mortality carried out in developing countries over this period^{18,26} report rates of 3.30 to 5.70 per 10,000 anesthetics. According to Lagasse (2002),³ the number of anesthesia-related deaths worldwide has not yet stabilized and one cannot detect trends in anesthesia safety until the causes of variation among studies have been fully understood and factored out. Lagasse highlights the fact that the causes of variation could represent real differences in anesthesia safety or just differences in the tools used to measure anesthesia-related mortality in the various studies.

Although anesthesia-related mortality has been reduced in recent decades, such a reduction is insufficient because, as articulated by Macintosh in 1948,³⁶ the ideal goal is that zero anesthesia-related deaths should occur. Unfortunately, anesthesia still contributes to major and avoidable adverse effects and deaths,³⁷⁻³⁹ and is still not completely safe in ASA I or II status patients.³

In developed countries, perioperative-related mortality also seems to have decreased from 133.4 per 10,000 anesthetics administered in 1948-1952⁴ and 188.9 per 10,000 in 1965-1969⁵ (Table 1) to fewer than 20 per

10,000 anesthetics^{3,17,22} and even fewer than 10 per 10,000 anesthetics^{14,16,19-21,23,25} (Table 2).

Nonetheless, Brazilian studies suggest no reduction in perioperative-related mortality rates. One study,²⁷ covering the period between 1982 and 1984, reported a perioperative mortality rate of 19 per 10,000 anesthetics, while studies performed in the last two decades reported higher incidences ranging from 21 to 51 per 10,000 anesthetics.^{28,31} Studies in developing countries have also reported high perioperative mortality rates (20.14 to 28.2 per 10,000 anesthetics).^{15,18,26} Certain pre-existing morbidities such as trauma, sepsis, and multiple organ failure, which seem to occur at a high incidence in Brazil,⁴⁰ and in developing countries as well,⁴¹⁻⁴³ have certainly influenced perioperative mortality rates. Thus, weaker clinical statuses of patients undergoing anesthesia seem to be the main factor contributing to the higher perioperative-related mortality rates reported by authors from developing countries in comparison with studies from developed countries.

The higher perioperative mortality rates observed among young adult males both in Brazil²⁹⁻³¹ and in several other countries^{20,22,24,35,44} can be explained by the fact that men are more predisposed to trauma, violence, and vascular disease than women. Poorer ASA physical status and emergency surgery have been reported as risk factors for perioperative mortality^{11,22,35} and are the only predictive factors of mortality after cardiac arrest.⁴⁵

Some investigators have reported an increased incidence of perioperative mortality in neonates and infants.^{11,14,21-23,30} Prematurity, congenital neurological disease, congenital heart disease, and other congenital defects place neonates and infants at a higher anesthesia risk than older children

and adults.⁴⁵ On the other hand, more recent studies^{20,24,30,34,45} have reported lower perioperative mortality rates in children from 1 to 12 years old.

Some reports^{11,12,17,21-23,28,35} have identified advanced age (70-80 years) as a risk factor. However, in one report,²¹ age itself was not found to be an independent risk factor. Anesthesia-related cardiac arrest and deaths in 70-80 year old patients seem to be increasing, especially during hip arthroplasty surgery.^{17,24,34} In France, the annual rate of anesthetic procedures between 1980 and 1996 increased from 6.6 to 13.5 per 100 people. Increases were greater in the elderly and in those with higher ASA physical status.⁴⁶ If this trend were global, it could indicate improvements in anesthesia safety because instead of an increase, a decrease in anesthesia-related mortality rates has been reported over the past 20 years in France.³⁵

Studies suggest that mortality is higher during general anesthesia than during neuraxial anesthesia.^{24,34,47,48} However, this may reflect the fact that patients with hemodynamic instability and a wider variety of more complex cases are surgically treated under general anesthesia. Such cases may include cardiac, thoracic, and neurological operators. Likewise, there may be a bias towards general anesthesia in emergency settings or for patients with coexisting medical conditions. Improved knowledge of neuraxial block physiology and the use of new and safer local anesthetics for the cardiovascular and central nervous systems, together with routinely used oxygen monitoring through pulse oximetry, have all decreased the frequency of major complications during neuraxial anesthesia.⁴⁹ On the other hand, mortality rates of zero have been observed during plexus block. Studies have shown that because there are no major respiratory and cardiovascular changes in plexus block mortality rates can be almost nil, and these low rates happened mainly after the introduction of newer local anesthetics with low myocardial toxicity.^{29,31,34,47}

Deaths caused by airway management failures seem to have decreased.^{11,20,35} Morray *et al.*⁴⁵ suggested that the predominance of cardiovascular events in anesthesia-related cardiac arrest and mortality may be related to the frequent use of pulse oximetry and capnography and monitoring hardware that may be more effective in preventing respiratory rather than cardiovascular events. In 24 cases reported by the Danish Closed Claims Registry, four cases were related to airway management and two to ventilation management.³⁸ A review of pediatric anesthesia malpractice claims showed that the frequency of respiratory events as primary causes of cardiac arrest has decreased from 51% in the 1970s to 41% in the 1980s and to 23% in 1990-2000.⁴⁷ On the other hand, cardiovascular events joined respiratory causes as major risk sources in the 1990s.⁵⁰

Medication-related problems have been reported as predominant factors in cardiovascular events as primary causes of mortality. Findings of the Pediatric Perioperative Cardiac Arrest (POCA) Registry reveal that the rate of medication-related cardiac arrests decreased from 37% (1994-1997) to 18% (1998-2004). This decrease was attributed to the increased use of sevoflurane, which is a less severe myocardial depressant than halothane.⁵¹ In addition, drug error in anesthesia practice is still a matter of concern and can lead to major problems and deaths.^{29,37}

In a study of 6,894 cases of the American Society of Anesthesiologists Closed Claims Project covering the period between 1975 and 2000, the proportion of claims for respiratory-related damaging events decreased, while the proportion of claims for cardiovascular-related damaging events increased so that by the period 1992-2000, they occurred at the same frequency (28%). This trend was associated with an increase in the use of pulse oximetry and end-tidal carbon dioxide monitoring. However, the increase in monitoring and the decrease in death or permanent damage rates seemed unrelated.⁵² Improvements should focus on these two most important areas in order to reduce the number of perioperative deaths. Continued education for anesthesiologists is crucial. However, one study demonstrated that poor practical application rather than lack of knowledge leads to critical incidents.⁵³ Major improvements in terms of perioperative morbidity and mortality seem possible with the application of simple anesthesia management principles, such as the routine use of an equipment checklist with documentation of the equipment check, direct availability of an anesthesiologist to lend a hand or troubleshoot when needed, no change of anesthesiologist during anesthesia, the presence of two anesthesia team members in emergency rooms, monitoring neuromuscular blockade, and when necessary, using muscle relaxant and opiate reversal to reduce perioperative morbidity and mortality after surgery and anesthesia.⁵³

A period of monitoring in a post-anesthesia care unit is now mandatory following all general, neuraxial, and regional anesthetics. For high-risk patients, continued monitoring in an intensive care unit may reduce anesthetic mortality. Inability to provide or failure to use these facilities may increase anesthesia-related mortality rates.

There are several methodological weaknesses associated with our study. For example, we fail to consider anesthesia-related mortality reported prior to 1966 because of the temporal limitations of the Medline database. It is, therefore, difficult to verify that all relevant studies predating the Medline database (1966) studies and even after this date have been considered.

In conclusion, our systematic review of the literature

confirms that perioperative mortality rates are higher in Brazil and other developing countries than in developed countries. Anesthesia-related mortality rates in Brazil and in developed countries are similar and lower than 1 per 10,000 anesthetics. Major risk factors for mortality are apparent for newborns, children under 1 year of age, the elderly, males, patients of ASA III or poorer physical status, emergency

surgeries, during general anesthesia, and in cardiac, vascular, thoracic, gastroenterologic, orthopedic, and pediatric surgeries. Medication-related cardiocirculatory events and airway management accounted for the majority of the cases of anesthesia-related mortality. These data may be useful in developing prevention strategies.

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