２０１２年6月２８日

公益社団法人日本麻酔科学会
理事長　森田　潔　殿

公益社団法人日本麻酔科学会
藤井善隆氏論文調査特別委員会
委員長　澄川　耕二

藤井善隆氏論文に関する調査特別委員会報告書

公益社団法人日本麻酔科学会藤井善孝氏論文調査特別委員会（以下　本学会と記す）は，会員である藤井善隆氏の論文について，2012 年 3 月 8 日に東邦大学が同氏の論文 8 編に倫理的問題があったと発表，続いて海外の複数の麻酔関連ジャーナルが同氏論文のデータに捏造の疑いがあるという論説を発表したことを受け，調査を行いました．

この度，その結果をまとめたので，調査特別委員会として以下の通り報告いたします．

藤井善隆氏論文に関する調査報告書

2012 年 6 月 28 日

公益社団法人日本麻酔科学会　藤井善隆氏論文調査特別委員会

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Ⅰ．事件発生の経緯(資料 1)

2011 年 7 月に海外ジャーナルから東邦大学あてに藤井氏論文の捏造疑惑調査依頼があった．これを受け，東邦大学は調査し，2012 年 3 月 8 日，同大学所属医師藤井善隆氏が牛久愛和総合病院で行ったとされる 8 論文の研究について，倫理委員会の承認を得ずに実施したとして，同氏を 2 月 29 日付けで諭旨退職処分としたことを英語版 HP で公表した．続いて，海外の複数の麻酔科関連ジャーナルが藤井氏論文の捏造疑惑に関する論説を発表，Anaesthesia では藤井氏関係論文 168 編（169 と公表されているが 1 編重複があるため実際は 168）について，統計学的に分析した結果，試験対象者の年齢，体格，血圧などの傾向が特定の範囲に集中し，平均的な分布と大きく異なっているとし，データの正しさに疑問を呈した．

以上を受け，本学会は 2012 年 3 月 10 日， 第 5 回理事会で藤井氏論文調査特別委員会を設置した．その後 2012 年 4 月 6 日 Joint Editors-in-Chief Request for Determination（23 ジャーナルの EIC 連名文書）が，日本国内 7 施設宛に送付された．調査対象論文は 192 編.（Request には 193 編と書かれてあるが， 1 編重複があるため実際は 192 編）6 月 30 日までに調査に対する回答がなければ，対象論文は Retract されるということである．

本報告書は，以上を受け設置された藤井氏論文調査特別委員会よる調査結果を報告するものである．

Ⅱ．藤井善隆氏の略歴

1981年4月　東海大学医学部医学科入学
1987年3月　東海大学医学部医学科卒業
1987年4月　東京医科歯科大学大学院医学研究科入学
1991年3月　東京医科歯科大学大学院医学研究科卒業
1991年4月～1995年6月　取手協同病院麻酔科
1995年7月～9月　東京医科歯科大学医学部麻酔蘇生科助手
1995年10月　カナダ　マギル大学
1997年1月～2005年6月　筑波大学　麻酔科　講師
2005年6月～2012年2月　東邦大学医学部　第一麻酔科　准教授

兼業期間

1989年頃～1991年3月，1995年7月～9月　取手協同病院　週１日程度
1997年～2011年2月19日　牛久愛和総合病院　不定期

Ⅲ．調査特別委員会の活動概要

１．委員会の構成

澄川耕二理事（副理事長，倫理委員長）を調査特別委員会委員長とし，下記のメンバーを調査委員とした．

委員長　澄川　耕二　（長崎大学医学部麻酔科　教授）
委　員　須加原一博　（琉球大学医学部麻酔科　教授）
野坂　修一　（滋賀医科大学医学部麻酔学講座　教授）
廣田　和美　（弘前大学医学部麻酔科学講座　教授）
浅井　　隆　（関西医科大学附属滝井病院麻酔科　講師）
山蔭　道明　（札幌医科大学麻酔科　教授）

２．委員会の活動

１）第１回調査委員会

2012 年 3 月 21 日，本学会神戸事務局で開催した．本件に関するこれまでの経緯と本学会としての対応の報告に続き，調査特別委員会としての活動計画案について協議した．本調査特別委員会では，論文研究の関係者からの面接調査，それらをもとにした調査報告書の作成，調査報告書の理事会への上申を活動項目とした．

面接調査は，調査特別委員会で検討した質問項目を中心に澄川，須加原，野坂，廣田の４委員が行い，収集した情報については，調査委員会全体で検討することとした．

２）主な共著者に対する面接調査および書面調査

2012 年 4 月 9 日，12 日，13 日，5 月 18 日，6 月 18 日の 5 日間にわたり，論文共著者の内，会員 14 名，非会員 1 名に対し面接調査を実施した．その他の共著者 21 名に対する書面調査を行った．

３）研究実施施設調査および協力要請

筑波大学附属病院　2012 年 4 月 18 日実施
JA とりで総合医療センター（以下取手協同病院（論文投稿当時））2012 年 5 月 31 日実施
牛久愛和総合病院　2012 年 5 月 31 日実施

４）第２回調査特別委員会

2012 年 5 月 18 日，本学会神戸事務局で開催した．面接調査報告書の内容について検討し，今後の調査の方針および方法について検討した．

これまでの論文，筑波大学での施設調査，面接調査において不一致がある点について確認すべく，論文の内容確認，施設調査データの整理等を行った．

５）第３回調査特別委員会

2012 年 6 月 26 日，本学会東京事務所会議室で開催した．面接調査等の結果を報告し，関係者の面接調査がすべて終了したことを確認した．その後，本学会理事会に提出する調査報告書を完成させた．

６）施設との情報交換

2012 年 6 月 27 日，筑波大学および東京医科歯科大学を訪問し，それぞれの調査委員会と情報交換を行った．

Ⅳ．調査方法

１．調査対象論文（資料 2，3）

藤井氏の全論文は 249 編であった．その内，原著論文 216 編，総説 20 編，症例報告 13 編であった．（資料 2）原著論文 216 編の内訳は，英文 205 編，和文 11 編であった．その内調査対象は，原著論文とし，マギル大学からでている 4 編を除いた 212 編とした．

（資料 3）

著者（筆頭・共著）となっている原著論文 212 編の内容別分類とその数

動物実験	犬：	59 編（筆頭：49　共著：10）
	モルモット：	1 編（筆頭：　0　共著：1）
臨床研究	術後悪心嘔吐：	109 編（筆頭：101　共著：8）
	プロポフォール血管痛：	15 編（筆頭：14　共著：1）
	その他	28 編（筆頭：17　共著：11）

臨床研究のうち大規模ランダム化比較試験：Randomized　Control Study（以下　RCT）を二重盲検法：Double Blind（以下　DB）で行ったとする論文　126 編

２．藤井氏への面接調査

2012 年 3 月 28 日，2012 年 6 月 4 日の 2 回にわたり面接調査を行った．以下の説明があった．

<u>第 1 回　2012 年 3 月 28 日</u>

① 捏造は 1 編たりともしていない．Anaesthesia の Special article は不当であり，全面否定のレターを投稿する（資料 4）．

② 論文の生データ，実験ノートは残っていないが，エクセルデータは一部ある．

③ 2000 年のAnesthesia & AnalgesiaでのDr. Krankeの捏造疑惑指摘は不当なものであり，反論を投稿したが掲載されなかった．

④ 犬の実験については東京医科歯科大と筑波大で行った．論文では，1 頭を 1 実験にのみ用いた．

⑤ 臨床研究については，取手協同病院，筑波大，牛久愛和病院で自分が麻酔を担当した症例で行った．1 症例を 1 研究の対象とし，エントリーの重複や，コントロールデータの使い回しは一切ない．患者のインフォームドコンセントは口頭で取得し，書面では取得しなかった．倫理審査員会の承認は得ていないが，取手と牛久では院長の承認を口頭で得，書面で得たのは 1 件のみであった．

⑥ 東邦大学解雇の理由は，「臨床研究の倫理審査を経ていない」ことであるが，牛久愛和総合病院で院長の承認を口頭で得ていた．

2012 年 6 月 4 日　第 2 回

① PONV の症例は，取手協同病院，筑波大学，牛久愛和総合病院でとった．

② カイトリルの研究はほとんど取手協同病院で行っていたが，市販薬として認められていたものは他の施設でやった場合もある．

③ データが複数の施設にまたがっても論文に記載しなかった．

④ 「論文上の犬の数と使用記録が大幅に違う」という指摘に対して「前回犬 1 頭を 1 実験に使用したと述べたが，実際には，1 頭で 5，6 回使用したこともあった．」

⑤ 「取手協同病院では，カイトリルの投与記録が 3 例しかなく，論文上の投与数とはならないがどうか」という質問に対して，「研究チャートには投与記録をつけていたが，麻酔記録には書かなかった」

⑥ 「Double Blind の論文に関して，内容から実験実行上 DB にするのは不可能な状況であるがどうか」との質問に対して，「共著者が割付，設定をした」

⑦ 「臨床研究において，所属施設の総担当症例数と論文上症例数がかけ離れており症例数の水増しもしくは，全く行っていない症例で論文を書いていないか」という質問に対して，「後者はなく，前者はわからない」

３．調査対象共著者

主な共著者（筆頭もしくは2番目または最後に名前が記載されている者）15名に対して面接調査を行った．その氏名，論文数は下記の通りである（論文数の多い順）．

豊岡秀訓（東京医科歯科大学，筑波大学）：113 編（筆頭論文 0，共著論文 113）
田中弘彦（取手協同病院）：109編（筆頭論文2，共著論文107）
斎藤祐司（東京医科歯科大学，取手協同病院）：38 編（筆頭論文 11，共著論文 27）
上村明（筑波大学）：23 編（筆頭論文 4，共著論文 19）
天羽敬祐(東京医科歯科大学)：18 編（筆頭論文 0，共著論文 18）
高橋伸二（筑波大学）：14 編（筆頭論文 3，共著論文 11）
板倉美千代（牛久愛和総合病院）：11編（筆頭論文0，共著論文11）
星拓男（筑波大学）：9 編（筆頭論文 2，共著論文 7）
宇田川友之（東京医科歯科大学）：7 編（筆頭論文 3，共著論文 4）
沼崎満子（筑波大学）：7 編（筆頭論文 5，共著論文 2）
大島勉（東京医科歯科大学）：5 編（筆頭論文 1，共著論文 4）
志賀由佳（筑波大学）：4 編（筆頭論文 1，共著論文 3）
鳴海豊（取手協同病院）：4 編（筆頭論文 0，共著論文 4）
筒井冨美（兵庫県立こども病院）：1 編（筆頭論文 1，共著論文 0）
横山訓典（東京医科歯科大学）：1 編（筆頭論文 0，共著論文 1）

共著者のうち3番目以降に名前が記載された者21名については，書面による調査を行った．

４．論文内容の検証

調査対象者および調査施設より入手した情報をもとに，次のように論文内容を検証した．

本人および共著者から提出された生データを元に論文データの再現性を検証した．また，筑波大学附属病院，JA とりで総合医療センター，牛久愛和総合病院に於いて麻酔台帳，麻酔記録，施設における手術術式別症例数，藤井氏担当の手術術式別症例数，動物実験計画書，動物実験センター犬持ち出し記録，劇毒物持ち出し記録，倫理委員会審査記録を閲覧しこれらの内容の調査を行った．これらを元に論文に記載された対象数と実際の対象者又は対象動物との照合，研究に用いた薬物の裏づけとなる使用記録との照合,調査対象者の証言をもとにした実験条件（二重盲検法等）の実行可能性の検証を行った．

Ⅴ．調査結果

１．捏造に関する判定

「捏造」の定義は，文部科学省研究活動の不正行為への対応ガイドラインから「存在しないデータ，研究結果等を作成すること」とした．

対象論文 212 編を検証した結果，次のように判定した．

A【捏造なし】

論文再現可能な生データがあり，対象数が確認できるもの

3 編（論文 No.101,112,150）

B【捏造あり】

対象数，実験条件，薬物投与記録のいずれかを満たさないもの

172 編（A と C を除く全論文）

C【その他】

捏造の有無を判断するに足る情報が得られなかったもの

37 編

(No.1,2,3,4,5,6,7,8,13,15,17,18,23,24,25,26,32,33,34,44,45,46,68,70,71,75,76,92,93,94,96,97,113,123,139,141,152)

２．判定の根拠

１）臨床研究について（資料 5～8）

（１）症例数から見た研究の実行可能性について（資料 5～7）

各論文に記載された症例数と，藤井氏の所属施設での担当症例数を調べ，論文記載症例数が正しいかどうか検証を行った．主な研究対象手術であった乳がん，婦人科（大手術），腹腔鏡下胆のう摘出，中耳，小児斜視，小児扁桃摘出，中絶，帝王切開の 1990 年～1995 年までの取手協同病院の施設症例数, 藤井氏担当症例数, 1997 年～2005 年までの筑波大学, 1997 年～2011 年牛久愛和総合病院藤井氏担当症例数の調査を行い，「資料　取手協同病院

症例数（以下，資料　取手症例数），筑波大学症例数，牛久愛和総合病院　症例数（以下，資料　牛久症例数）」としてまとめた．

資料 6 より，臨床研究の主な場であった，取手協同病院での藤井氏が在籍した 1990 年～1995 年の主な研究対象手術件数を見ると，乳がんの担当症例 59 例に対して臨床研究論文上症例数 700 例（取手協同病院施設症例 119 例），婦人科（大手術）252 例に対して 1368 例（施設症例 589 例），腹腔鏡下胆のう摘出術 80 例に対して 540 例（施設症例 107 例），中耳 13 例に対して 500 例（施設症例 41 例），小児斜視 5 例に対して 400 例（施設症例 15 例），小児扁桃摘出術 26 例に対して 260 例（施設症例 81 例），中絶 2 例に対して 80 例（施設症例 4 例），帝王切開 6 例に対し 220 例となっている．

また，取手協同病院，筑波大学，牛久総合病院（資料 6，7，8）の藤井氏合計担当症例数をみても，乳がん 157 例（内訳：取手 59 例，筑波 86 例，牛久 12 例）に対して，論文上総症例数は，950 症例，小児斜視（取手，筑波）5 例（内訳：取手 5 例，筑波 0 例）に対して，論文上総症例数は，520 例となっている．その他の研究対象手術症例に関しても腹腔鏡下胆のう摘出術藤井氏担当症例（取手，筑波，牛久）137 例（内訳：取手 80 例，筑波 44 例，牛久 13 例）に対して，論文上症例数は，1524 例となっている．

上記の調査内容から，藤井氏の担当症例数はもとより，取手協同病院については，施設症例数より論文上症例数が多くなっており，研究の実行は不可能である．

（2）論文内に症例データ取得期間が記載されている論文について

212 論文のうち，症例データ取得期間が記載されている論文について調査を行った．資料 3 の No.129,No.161 の 2 編が該当論文である．

No.129 の論文は，筑波大学で 1999 年 9 月～2001 年 3 月に行い，研究対象手術は中絶となっており，論文上症例 120 例であった．筑波大学でその期間の藤井氏担当中絶症例を調べたところ，32 例であった．また，その期間の筑波大学全体の中絶症例は，99 例であった．共著者である上村氏は共著者であること，論文内容，掲載誌等の認識は全くないとのことであった．

No.161 の論文は，取手協同病院で 2002 年～2004 年に行い，研究対象手術は子宮摘出，対象年齢 33 歳～66 歳となっており，論文上症例 100 例であった．取手協同病院でその期間の藤井氏担当症例を調べたところ 3 例であった．また，カイトリルを投与した内容となっているが，取手協同病院でカイトリル投与を確認できた記録（3）投与薬剤から見た研究実行可能性について参照）は 2 例であった．藤井氏は，カイトリル投与記録について，研究チャートにはつけていたが，麻酔記録には書かなかったと述べている．また，市販薬として認められているものについては，麻酔記録に記載するが，研究的なスタディードラックについては書かなかったと述べている．共著者である田中氏は，上村氏と同様共著者であるという認識は全くないとのことであった．

（3）投与薬剤から見た研究実行可能性について（資料 8）

藤井氏の臨床研究の主な研究テーマである制吐剤の投与実態を調査した．取手協同病院

では以下の通りであった.

取手協同病院薬剤使用歴（麻酔台帳より）

	1992 年	1993 年	1994 年
カイトリル	0	2	0
プリンペラン	6	8	0
ドロペリドール	2	0	0

＊カイトリル：グラニセトロン
＊プリンペラン：メトクロプラマイド

現カイトリル販売会社（2001 年より）である中外製薬に，取手協同病院のカイトリル納入実績を聞いたところ，2000 年以前の販売会社であるスミスクライン社から継承された納入関連の書類は存在せず不明であった.

また, 筑波大学の甲状腺, 中絶, 胆のう摘出手術それぞれの投与実態を調べたところ 1998 年から 1999 年には投与歴はなかった.

上記の調査内容から，グラニセトロンの投与による実験は不可能であり，グラニセトロンの 69 編の研究は，実行不可能である.

（4）無作為化比較試験，二重盲検法：Randomized　Control Study，Double Blind（以下 RCT DB）論文について

RCT DB の論文は 126 編あり，RCT DB が論文上どおり実行可能であるか検証した.

No.11 の論文については，取手協同病院で行った研究であるが，挿管する相手が高血圧かどうか，ブラインドで行っていることになっている．この論文では，麻酔の責任者であった藤井氏が麻酔を実施していると論文内に記載があるが, 挿管する相手が高血圧かどうかをブラインドで行うことは，困難である．本来，RCT DB 実施者が相手の素性を認識できないことを意味するものであり，LMA か挿管かというのは，ダブルブラインドとはいえない．この研究の場合，過去高血圧の状態であったかどうかがブラインドの対象となり, この研究の成立は極めて困難であり, 成立するとすれば，倫理的に疑わしいということになる．藤井氏が RCT DB について理解していないか，意図的に論文に記述したものと考えられる．その他の論文に関しても，施設の勤務人数，共著者の説明から鑑み，RCT DB で行うことは不可能である．また，単著論文の Double Blind の論文についても実行可能であるか検証した．No.179 の論文については，DOSE を Double Blind で行ったと述べたが, 1 名では実行不可能である. 共著者の面接においても，無作為割付，二重盲検法に協力したと述べた共著者は存在しない.

2）動物実験について

（1）犬の実験実行可能性について（資料 9）

犬の実験は，東京医科歯科大学，筑波大学で実施している.

東京医科歯科大学では，論文上の犬の総数 350 頭であったが，犬の使用記録等が一切残っておらず，実際の使用数を示す記録はない．面接調査により，大学院時代の 2 年間週 1 日研究日があり，実験は大学院時代 2 年間，取手協同病院時代 4 年間実験をおこなっていた．論文上の犬の頭数 350 頭　使用可能頭数週 1 回として最大 312 頭となり，東京医科歯科大学で行われた実験において，捏造と断定する根拠はない．

筑波大学については，資料 10 にあるように，筑波大学動物実験センター実験用犬搬入出記録及び, 動物実験センター犬持ち出し記録の頭数を照合した. 記録が残っていない, 1997, 1998，2000，2001 年については，実験可能日から算出した推定最大値を用いた．勤務を開始したのは,1997 年であり,1998 年の論文上の犬の頭数が使用頭数の範囲内に収まるが, 1999 年からは, 論文上の犬の頭数が使用頭数を上回り, 年を追う毎にこの差は大きくなり, 全体では，論文上犬の総数が 913 頭，使用総数は 163 頭と大きく食い違い，捏造があるのは明らかである．

（2）実験期間明記論文について

No.210 の論文は，筑波大学において 2008 年 7 月から 12 月の 6 ヶ月間に 21 頭の犬を用いて実験をしたことが明記されている．実際には，この間に著者が筑波大学で実験をした事実はなく，また犬を使用した事実もない．すなわち完全な捏造である．

３．倫理上の問題について

１）施設倫理委員会の審査について

各施設において倫理委員会の審査を受けたことは一度もない．関連する書類としては，取手協同病院の病院長名で 1995 年 6 月 30 日に発行された制吐剤の研究の研究承諾書 1 枚のみである．

２）インフォームドコンセントについて（以下，IC）

藤井氏の面接調査により，全ての論文の IC は口頭でとったとのことであり，書面は残っていない．No.208 の論文については，IC を書面でとったとの記載があったが，本人に確認したところ，海外ジャーナルが勝手に written approval に変更したとのことであった．

４．共著者の論文サインについて

藤井氏の投稿論文の EIC に連絡し, 投稿論文の共著者も含めたサインの状況をしらべた. 2 誌から連絡があり，その内の 1 誌については，該当者に確認したところ，サインしたとのことであった．残り 1 誌については，2 名の共著者がいたが，2 名ともサインはしていないと明言した．

５．論文業績の利用について

藤井氏は，これらの論文業績を，学内での業績評価，大学教員ポストの獲得，教授選考への立候補，公的研究費獲得，本学会学会賞への応募等に利用していた．

６．共著者の役割について（資料 10）

共著者について，調査した限りにおいては，データの捏造を指示，協力した者はいなかった．ただし，下記に挙げる 3 名の共著者については，突出して共著論文数が多かったため，その背景について個別に述べる．

・豊岡秀訓氏　113 編（筆頭論文 0，共著論文 113）

東京医科歯科大時代から筑波大時代まで長期に亘って直接的指導の立場にあった上司，責任著者であり，捏造に関与しなかったとはいえその責任は重大である．その理由は，①投稿論文にサインしていることからその存在を認識していた，②筑波大学臨床医学系業績集に藤井氏の論文が 85 編掲載されている(内, 筆頭 69 編, 共著 16 編)を掲載している, ③2000 年の時点でAnesthesia & Analgesiaに掲載されたDr. Krankeの捏造疑惑（資料 10）を無視した，ことである．

・田中弘彦氏　109編（筆頭論文2，共著論文107）

施設の上司としてデータ捏造を指示したり，協力したことはなかった．藤井氏が取手協同病院を退職した 1995 年より後は，本人との接触は一切なかったが，1996 年以降 87 編の論文の共著者となっている．これらの論文は，田中氏の承諾は得ず発表されたものである．1998 年にペインクリニックで開業し，麻酔関連の論文に目を通すことはなく気づかなかった．

・斎藤祐司氏　38 編（筆頭論文 11，共著論文 27）

藤井氏とは全く別に研究を行っており，研究自体に協力したことはない．それにも関わらず，共著者となっているのは，お互いに業績を増やすために論文に名前をいれあうとする約束を結んでいたからである．

・その他の共著者

上記の不正に関し，調査した限りにおいては，データの捏造への関与はなかった．論文を業績として利用していた者，論文の存在に気づいていたが放置した者，論文の存在を知らなかった者など様々であった．

Ⅵ．結論

１．捏造のなかった論文は，3 編，捏造があった論文は，172 編，その他（捏造の有無を判断するに足る情報が得られなかった）の論文は，37 編である．

２．捏造は 19 年間にわたって行われた．

捏造論文の発表は 1993 年の臨床研究 2 編を皮切りに 2011 年まで行われた. すでに 1994 年にはランダム化比較試験二重盲検法の論文スタイルを確立し，一流英文ジャーナルへの発表を果たし，以後そのスタイルを継続した．

３．捏造論文は一部から完全なものまである．

研究対象の動物または症例が実在し，研究を実施したのは初期の論文のみであり，それ以外の大多数については研究対象が 1 例も実在せず，薬剤の投与も行われず，研究自体が全く実施されなかったものである．即ちあたかも小説を書くごとく，研究アイデアを机上で論文として作成したものである．

４．論文の構成には共通の特徴がある．

論文がアクセプトされるための方策として，「膨大な数の症例」を対象に，「無作為化比較試験（RCT)」を「二重盲検法（double blind)」で実施した，とするのがほとんどの論文に共通する構成上の特徴であり，タイトルにも用いていた．126 編の RCT　DB が全て捏造である．

５．研究実施の施設と期間を巧妙に暈した．

通常は研究実施施設と期間を論文に明記するものである．藤井氏の場合，自分が所属する施設において研究をしていないのに，次々に論文を発表すると同僚に疑われるため，「データは前に勤務していた病院またはアルバイト先の病院でとったもの」であるかのように装っていた．実際，論文には研究施設と研究期間を明記せず，倫理委員会の施設名も入れていない．また共著者に他施設の医師を入れることにより，実施施設が複数にまたがっているかのように装った．これらの方策は長期に亘って捏造の発覚を免れるのに有効であった．

６．論文の捏造は単独で行ったものである．

論文には多くの共著者が存在するが，捏造と知ってこれに手を貸した共著者はいない．論文は単独で作成したものであり，単著で投稿する方が容易であったが，そうしなかった理由は捏造の発覚を防ぐためであった．実際 6 月に出した Anaesthesia へのレターでは「私ひとりで行った研究ではない」ことを捏造でない理由として挙げている．

７．論文投稿のカバーレターに共著者自身がサインしていないものがある．

近年，ジャーナルは共著者全員のサインを要求するようになっているが，共著者の多くはサインをしていない．藤井氏自身も「共著者のサインはジャーナルから求められなかったので入れていない」としている．本委員会がジャーナルから入手したカバーレターの 1 通には藤井氏以外の共著者 2 名のサインがあったが，本人の自筆でないことを確認している．

８．共著者の責任は重大なものから一切ない者まで多岐に亘る．

東京医科歯科大時代から筑波大時代まで長期に亘って直接的指導の立場にあった上司は豊岡教授であり，捏造に関与しなかったとはいえその責任は重大である．他の共著者については，いずれも捏造への関与はないが，論文を業績として利用していた者，論文の存在

に気づいていたが放置した者，論文の存在を知らなかった者など様々である．論文の多くは共著者に承諾を得ず投稿され，別刷も共著者に渡されていなかった．従って論文の存在に気づいていない共著者も多い．裏返せば，自分の論文に関心が薄く，了承なしに共著者にされても疑念を抱かないしクレームをつけない人を，藤井氏は選んだといえる．

９．藤井氏は論文業績を多方面に利用していた．

論文業績は，筑波大講師や東邦大准教授に採用されるのに必須のものであった．公的研究費を獲得した．日本麻酔科学会学会賞にも 5 度応募したが選外であった．企業主催のセミナーの講師を 2 度務め講師謝礼を受け取った．

Ⅶ．再発防止について

以下の対策を早急に周知し，意識の改善を図る．

- 国内外ジャーナルの査読機能を高めることに資するべく,本件の全容を日本語および英語で公表する．
- 医学研究施行と報告上の倫理規定について学術集会，セミナー等を毎年開催し，周知する．
- 研究施設の責任者，筆頭著者，共著者の医学研究施行の責務について改めてガイドライン等でまとめ，周知する．
- 疑わしい論文に関して，情報提供を受けつけ，調査する体制を学会内で作ることを検討する．

東邦大学英語ホームページ掲載

Disciplinary Decision concerning Dr. Yoshitaka Fujii

<< News/Information

Dr. Yoshitaka Fujii was an associate professor of Anesthesiology, Toho University Faculty of Medicine. The credibility of Dr. Fujii's 9 publications (see list below), which were published in foreign journals under the name of Toho University, was put in doubt in August, 2011. Toho University, therefore, organized an investigation committee in September, 2011, and made a searching inquiry into their credibility. The committee reached the following decision:

Since all of Dr Fujii's clinical studies that appeared in these 9 publications were conducted at Ushiku Aiwa General Hospital, which has no relation to his research activity in Toho University, the investigation committee contacted the head of the hospital. As far as the head of the hospital knows, there was only one clinical study listed by Dr. Fujii as having been conducted at the hospital. The other eight clinical studies were conducted without any ethics committee's approval, and this was judged sufficient to decide that 8 of his publications (No. 2 to 9) should be retracted since they did not conform to the global standard of ethics for clinical studies. After the investigation, the committee asked Dr. Yoshitaka Fujii and his co-author, Dr. Michiyo Itakura, to explain the whole circumstances. Dr. Fujii admitted that the clinical studies were done without any ethics committee's approval. Dr. Itakura, however, was not involved in this misconduct. Dr. Yoshitaka Fujii sent letters of retraction to the affected journals. We organized a disciplinary committee and decided that a disciplinary dismissal was appropriate for Dr. Fujii, effective from February 29, 2012. Dr. Fujii has already been dismissed from Toho University.

Masaru Kuroda, M.D. & Ph.D.
Dean
Toho University Faculty of Medicine

List of Dr. Fujii's 9 publications which were put in doubt

1. Fujii Y, Itakura M.: Efficacy of the lidocaine/flurbiprofen axetil combination for reducing pain during the injection of propofol. Minerva Anestesiol. 2011 Jul;77(7):693-7.
2. Fujii Y, Itakura M.: Antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. Otolaryngol Head Neck Surg. 2011 Feb;144(2):206-9.
3. Fujii Y, Itakura M.: A prospective, randomized, double-blind, placebo-controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery. Clin Ther. 2010 Aug;32(9):1633-7.
4. Fujii Y, Itakura M.: Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2010 Mar;24(3):692-6.
5. Fujii Y, Itakura M.: A comparison of pretreatment with fentanyl and lidocaine preceded by venous occlusion for reducing pain on injection of propofol: a prospective, randomized, double-blind, placebo-controlled study in adult Japanese surgical patients. Clin Ther. 2009 Oct;31(10):2107-12.
6. Fujii Y, Itakura M.: Low-dose propofol to prevent nausea and vomiting after laparoscopic surgery. Int J Gynaecol Obstet. 2009 Jul;106(1):50-2.
7. Fujii Y, Itakura M.: Pretreatment with flurbiprofen axetil, flurbiprofen axetil preceded by venous occlusion, and a mixture of flurbiprofen axetil and propofol in reducing pain on injection of propofol in adult Japanese surgical patients: a prospective, randomized, double-blind, placebo-controlled study. Clin Ther. 2009 Apr;31(4):721-7
8. Fujii Y, Itakura M.: Comparison of propofol, droperidol, and metoclopramide for prophylaxis of postoperative nausea and vomiting after breast cancer surgery: a prospective, randomized, double-blind, placebo-controlled study in Japanese patients. Clin Ther. 2008 Nov;30(11):2024-9.
9. Fujii Y, Itakura M.: Comparison of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, parallel-group, placebo-controlled study. Clin Ther. 2008 Feb;30(2):280-6.

東邦大学日本語 HP 掲載

東邦大学医学部における臨床研究の倫理規範悖反について

東邦大学では、麻酔科学第一講座に所属する藤井善隆准教授が発表した学術論文の記載について、科学的合理性および倫理的妥当性に重大な疑義があるとの通報があったことを受けて、調査委員会を設置して調査を行ってきました。

この調査の結果、藤井准教授が発表した8つの論文について臨床研究に関する倫理規範に悖反する事実があったと認定しましたので公表します。
この事実に基づき、懲戒委員会で処分を検討し、平成 24 年 2 月 29 日付けで諭旨退職処分と致しました。

Anaesthesia 2012 doi:10.1111/j.1365-2044.2012.07128.x

Special Article

The analysis of 169 randomised controlled trials to test data integrity

J. B. Carlisle

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Summary

The purpose of this study was to use some statistical methods to assess if randomised controlled trials (RCTs) published by one particular author (Fujii) contained data of unusual consistency. I searched seven electronic databases, retrieving 169 RCTs published by this author between 1991 and July 2011. I extracted rates for categorical variables and means (SDs) for continuous variables, and compared these published distributions with distributions that would be expected by chance. The published distributions of 28/33 variables (85%) were inconsistent with the expected distributions, such that the likelihood of their occurring ranged from 1 in 25 to less than 1 in 1 000 000 000 000 000 000 000 000 000 000 000 (1 in 10^{33}), equivalent to p values of 0.04 to $< 1 \times 10^{-33}$, respectively. In 142 human studies, 13/13 published continuous variable distributions were inconsistent with expected, their likelihoods being: weight < 1 in 10^{33}; age < 1 in 10^{33}; height < 1 in 10^{33}; last menstrual period 1 in 4.5×10^{15}; baseline blood pressure 1 in 4.2×10^{5}; gestational age 1 in 28; operation time < 1 in 10^{33}; anaesthetic time < 1 in 10^{33}; fentanyl dose 1 in 6.3×10^{8}; operative blood loss 1 in 5.6×10^{9}; propofol dose 1 in 7.7×10^{7}; paracetamol dose 1 in 4.4×10^{2}; uterus extrusion time 1 in 33. The published distributions of 7/11 categorical variables in these 142 studies were inconsistent with the expected, their likelihoods being: previous postoperative nausea and vomiting 1 in 2.5×10^{6}; motion sickness 1 in 1.0×10^{4}; male or female 1 in 140; antihypertensive drug 1 in 25; postoperative headache 1 in 7.1×10^{10}; postoperative dizziness 1 in 1.6×10^{6}; postoperative drowsiness 1 in 3.8×10^{4}. Distributions for individual RCTs were inconsistent with the expected in 97/135 human studies by Fujii et al. that reported more than two continuous variables, their likelihood ranging from 1 in 22 to 1 in 140 000 000 000 (1 in 1.4×10^{11}), compared with 12/139 RCTs by other authors. In 26 canine studies, the distributions of 8/9 continuous variables were inconsistent with the expected, their likelihoods being: right atrial pressure < 1 in 10^{33}; diaphragmatic stimulation (100 Hz) < 1 in 10^{33}; pulmonary artery occlusion pressure < 1 in 10^{33}; diaphragmatic stimulation (20 Hz) < 1 in 10^{33}; heart rate 1 in 6.3×10^{10}; mean pulmonary artery pressure 1 in 2.2×10^{14}; mean arterial pressure 1 in 6.3×10^{7}; cardiac output 1 in 110. Distributions were inconsistent with the expected in 21/24 individual canine studies that reported more than two continuous variables, their likelihood ranging from 1 in 345 to 1 in 51 000 000 000 000 (1 in 5.1×10^{13}).

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Patterns are useful because they tell us something about the processes that create them. When patterns deviate from the expected, we know that something unusual has happened. Random allocation of individuals from a population into different groups distributes both categorical and continuous variables in predictable patterns, the centre, spread and shape of which are necessary consequences of the interaction between the sampled population and the sampling method.

For example, the variation in the means of continuous variables, such as age, depends upon: (i) the mean age of the sampled population; (ii) the population's age distribution; and (iii) the size of the sample. The distribution of mean values for each continuous variable is normal (Gaussian), unless the population variable is both very asymmetric ('skewed') and the samples have been small (often quoted as < 30 individuals). The distribution of means in such cases will be slightly skewed and may cluster more or less tightly around the population mean.

Similarly, the variation in the proportions of binomial characteristics, such as sex, depends upon: (i) the proportions of each sex in the sampled population; and (ii) the size of the sample. The shape and asymmetry of binomial distributions change with these two variables.

Significant deviation from the expected occurrences of one binomial characteristic in the outcomes reported by one particular anaesthetic researcher was publicised by Kranke et al., commenting that: 'Reported data on granisetron and postoperative nausea and vomiting by Fujii et al. are incredibly *nice*!' [1]. Kranke et al. concluded by observing: '…we have to conclude that there must be an underlying influence causing such incredibly nice data reported by Fujii et al.'

Kranke et al. had looked at 47 randomised controlled trials (RCTs) of antiemetics to prevent postoperative nausea and vomiting (PONV), published between 1994 and 1999 by Dr Yoshitaka Fujii and colleagues (references 1–47; Appendix S1; available online, please see details at the end of the paper). Eighteen of these RCTs had reported postoperative rates of headache. Ten had reported the same rate of headache in every group; for instance, in one paper, Fujii et al. reported that they had randomly allocated 270 women to one of six groups (reference 1; Appendix S1). Eighteen of the 270 women had postoperative headaches: 3/45 in each of the six groups. Table 1 shows the reported and expected (i.e. by chance) rates of headache in such patients.

Table 1 Example of the methods used in my analysis. Number of women with headache in groups of 45 women, as reported in a single study (reference 1; Appendix S1) and as would be expected by chance.

Women with a headache in a group of 45	Groups reported with this incidence of headache in this study	Groups expected with this incidence if headaches were distributed randomly across groups
0	0	0.3
1	0	0.9
2	0	1.4
3	6	1.4
4	0	1.0
5	0	0.6
6	0	0.3
7	0	0.1

Kranke et al. proceeded to reject the null hypothesis that 10/18 RCTs would report homogenous rates of headache by chance, calculating a probability of 6.8×10^{9}, or 1 in 147 million. My slight concern is that this indirect calculation confused the probability of a particular incidence's occurring, with the probability that this incidence is consistent with the expected binomial distribution. Kranke et al. calculated the first probability, but it is the second that I am more interested in. This turns out to be ~1 in 5600 for the distribution of headache reported in all 18 RCTs that Kranke et al. analysed: more than Kranke's estimate, but still 280 times smaller than the $p < 0.05$ threshold conventionally regarded as statistically significant.

Kranke et al. had concluded that it was more likely that an 'unnatural mechanism' had obliterated the expected binomial distribution. Moore et al. mention these 'suspect' data in their editorial on scientific fraud [2].

My purpose in this study was to extend the statistical analysis of papers, begun by Kranke et al., to all RCTs published by Fujii. Identification of unnatural patterns of categorical and continuous variables would support the conclusion that these data depart from those that would be expected from random sampling to a sufficient degree that they should not contribute to the evidence base.

Methods

I searched the following databases (author 'Fujii') between 1991 and July 2011: the Cochrane Central

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Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; ISI WOS; LILAC; and INGENTA. I included RCTs authored by Dr Yoshitaka Fujii, identified as working at the University of Tsukuba Institute of Clinical Medicine, the Tokyo University Medical and Dental School, the Toride Kyodo General Hospital or the Toho University School of Medicine (with Fujii in any position in the list of authors). I analysed the integrity of the data in these RCTs and compared them with 366 RCTs by other authors (Appendices S2–S6; available online) [3].

From the retrieved studies, I extracted the following data: the number of participants or animals in each group; all continuous variables reported as mean (SD), for example age; and all categorical variables, such as the number of women. I included variables measured before or after exposure to the allocated intervention, as long as they had been unaffected by the exposure.

Appendix A details the generation of expected categorical and continuous distributions and their subsequent statistical analysis, whilst an example illustrates the method at the beginning of the Results section, below. Broadly, the analysis is based on two principles focused on the spread of values around the most common value (rather than simply comparing two averages). The first principle is for categorical distributions, which can best be understood by considering the results of tossing two coins: the most likely outcome (50%) is head and tail while two heads or two tails is less likely (25% each). The probability of departures from these frequencies (e.g. finding that two tails occur 75% of the time in a dataset) can be calculated. In this example, one knows that for a single coin, there is an equal chance a head and a tail will be tossed, so one knows the expected shape of the binomial distribution for two coins. For the categorical variables analysed in this paper, one does not know the expected rate for each outcome – for instance, how many men or women one might expect in a sample of patients having cholecystectomy. Fortunately, the answer is given for each study by each study itself – if in total 80/100 patients randomly allocated to five groups are women, then one would expect a binomial distribution that peaks at a female distribution of 16/20 women per group. In this important way, my analysis also looks at the spread of proportions in each group, not just the peak value.

The second principle of analysis, for continuous variables, is known as the 'central limit theorem'. If we calculated the mean height of people in a sample, performed repeated sampling of other groups of people, and then plotted a series of these means, we would obtain a normal curve, even if the distribution of heights within the sampled population was not normal. The standard deviation of this curve can be estimated from the sample standard deviation and is called the standard error of the mean (SEM). The SEM is a measure of the extent to which the sampled means vary from the (true) population mean. The SEM is rather like a standard deviation of the sample means, illustrating their variation. Just as for binomial characteristics, the focus of the analysis in this paper is the spread of means, not the peak value. Authors occasionally mislabel standard deviations (SDs) as standard errors of the mean (SEMs), so I checked whether substitution of one by the other resolved apparently abnormal distributions.

In this paper, each RCT is its own standard: the expected distributions of categorical rates and continuous means for each RCT were generated from within the same RCT. For categorical variables, this mathematical coupling of expected-to-reported measurement actually reduces the power of my analysis to identify aberrant distributions, because the expected result is dependent upon the observed result. In other words, my method is 'conservative' and any finding of aberrant distributions using this technique suggests extremely aberrant data distribution. In contrast, my method of analysis of continuous variables can overestimate clustering of means in small samples due to imprecision of the reported means and SDs or a population distribution that might be skewed. I therefore applied a somewhat arbitrary (but again intentionally conservative) adjustment to reduce any clustering (Appendix A). Any finding of clustering after adjustment indicated that the data were strikingly clustered. Furthermore, I subjected to the same analysis 366 RCTs by authors other than Fujii et al.

Results

I identified and retrieved 169 RCTs published by Fujii and colleagues between 1991 and July 2011: 142 in humans (13 734 participants); 26 in dogs (688 mongrels); and one in guinea pigs (14 animals) (references 1–169; Appendix S1). This alone is a remarkable research output

– over 600 patients per year – and offers much useful material for analysis (Fig. 1). The focus of the human RCTs was prevention of PONV in 92 (54%), pain on injection of propofol in 14 (8%), treatment of PONV in 13 (8%), neuromuscular blockade in 11 (7%), the cardiovascular response to airway manipulation in 9 (5%), and epidural analgesia, middle cerebral artery perfusion and postoperative hypoxaemia in one each (1%). Drug effects on diaphragmatic contractility were the focus of the guinea pig study and 23 canine RCTs (24%), whereas the remaining 3 (2%) canine studies focussed on haemodynamic effects of drugs.

In addition, I analysed 366 other RCTs: 126 RCTs by other authors that reported postoperative rates of headache following prophylactic antiemesis (Appendix S2; available online); 31 RCTs by other authors of PONV prophylaxis with granisetron (Appendix S3; available online); 100 RCTs by other authors of rescue rates for droperidol and metoclopramide (Appendix S4; available online); 65 additional RCTs by other authors that reported rates of side effects after PONV prophylaxis (Appendix S5; available online); 145 RCTs by other authors of PONV prophylaxis reporting age, height or weight of participants (Appendices S2–S6). Some RCTs contributed to more than one analysis.

An example

The following single study serves as an example to illustrate the analyses of categorical and continuous variables. In one paper, Fujii et al. reported the response of 100 adults with PONV (20 per group) to placebo or one of four intravenous doses of granisetron (10, 20, 40 or 80 $\mu g.kg^{-1}$) (reference 90; Appendix S1). Table 2 lists the seven reported continuous variables and Table 3 lists the standardised differences between the mean of each group and the estimated population mean for these variables (see Appendix A for how to obtain the data in Table 3 from the original data in Table 2). Figure 2 presents histograms of the 35 standardised differences from Table 3. Each bar is 0.25 standardised differences wide with a height determined by the number of differences within each bar. The superimposed red curve (left graph) represents the expected distribution of standardised differences, the 'standard curve', with a mean of zero, a standard difference of one and a peak probability density at the mean of 0.40. The superimposed black curve (middle and right graphs) is the probability density curve generated by the data: the statistical test is between the variances of red and black curves. The result was that there was a significantly greater clustering of the actual data around zero than would be expected by chance

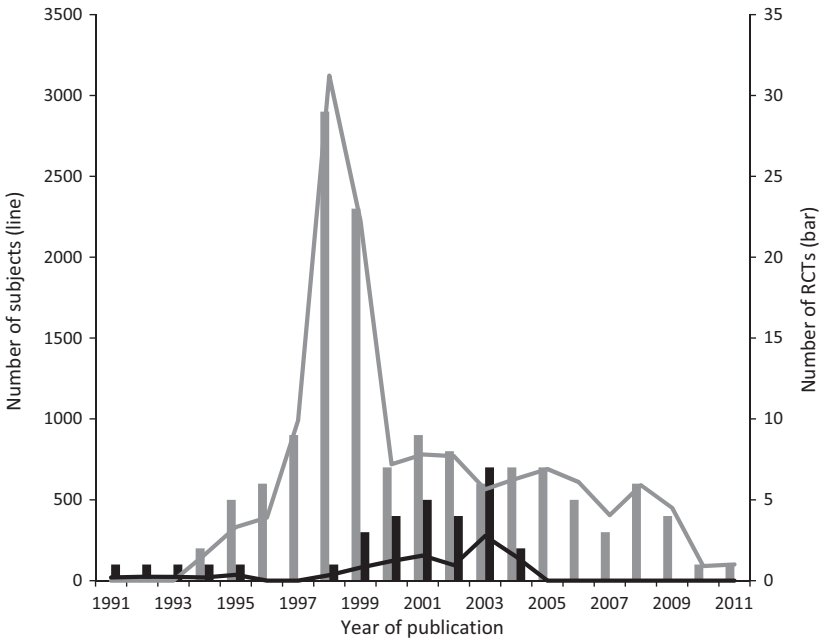

Figure 1 Histogram showing the number of RCTs published per year by Fujii et al. (vertical bars, human RCTs ■, animal RCTs ■) and the number of subjects these RCTs reported (human grey line, animals black line).

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Table 2 Means ($\bar{m}$) for continuous variables reported for the five groups of a study of granisetron by Fujii et al. (reference 90; Appendix S1). Values are mean (SD).

	Granisetron dose; μg.kg^{-1}					
	Placebo (n = 20)	10 (n = 20)	20 (n = 20)	40 (n = 20)	80 (n = 20)	Population mean (μ)
Age; years	46 (8)	47 (7)	45 (11)	47 (10)	50 (11)	47 (9)
Height; cm	159 (10)	158 (9)	155 (11)	157 (10)	159 (9)	158 (10)
Weight; kg	57 (7)	57 (9)	54 (7)	54 (8)	58 (8)	56 (8)
Surgical time; min	86 (35)	92 (31)	83 (34)	87 (36)	92 (27)	88 (33)
Anaesthetic time; min	106 (35)	117 (33)	106 (36)	112 (37)	118 (29)	112 (34)
Fentanyl dose; μg	103 (79)	98 (73)	93 (73)	98 (79)	105 (86)	99 (78)
LMP; days	16 (3)	16 (3)	16 (3)	16 (3)	16 (3)	16 (3)

LMP, last menstrual period.

Table 3 Calculated standardised mean differences (($\bar{m}-\mu$)/SEM where SEM = SD/$\sqrt{20}$; see Appendix A) for the continuous variables presented in Table 2.

		Granisetron dose; μg.kg^{-1}				
	SEM	Placebo (n = 20)	10 (n = 20)	20 (n = 20)	40 (n = 20)	80 (n = 20)
Age; years	2.10	−0.48	0.00	−0.95	0.00	1.43
Height; cm	2.19	0.64	0.18	−1.19	−0.27	0.64
Weight; kg	1.74	0.57	0.57	−1.15	−1.15	1.15
Surgical time; min	7.29	−0.27	0.55	−0.69	−0.14	0.55
Anaesthetic time; min	7.60	−0.76	0.68	−0.76	0.03	0.82
Fentanyl dose; μg	17.44	0.21	−0.08	−0.37	−0.08	0.32
LMP; days	0.67	0.00	0.00	0.00	0.00	0.00

LMP, last menstrual period.

(p = 0.0017), as demonstrated by comparison with the standard curve. This was the case even with the variable 'last menstrual period' (LMP) removed (p = 0.016; please see the Discussion section, below, concerning the invariance of LMP). However, in this example, adjustment of the variance (see Methods, Appendix A) made the distribution consistent with the expected (p = 0.06). Subsequent figures are illustrated with the comparative red standard normal curve.

Table 4 lists the number of participants in each group for the six reported binomial variables in the same study, and Fig. 3 presents histograms of reported and expected rates for these binomial variables. For instance, 40/100 participants were women, which is the best estimate of the proportion (0.40) of women in the population from which 100 participants were drawn. The expected binomial distribution of this variable is therefore determined by the rate of 0.40 and the sample size. Summation of the binomial distributions for the 6 variables in Table 4 results in the expected distribution depicted by white bars in Fig. 3. The reported distribution was no different from that expected (p = 0.13). For this published study taken in isolation, therefore, my conclusion was that it did not contain data of unusual consistency.

Summary of human studies

The approach explained above was applied to perioperative continuous and categorical variables reported in 142 human RCTs (studies specified in the Tables 5–9). Figures 4–7 show the histograms of standardised mean difference for some of the reported continuous variables, illustrating that the reported clustering around zero was more extreme than expected by chance. Recall that for continuous variables, the SDs should be ~1.0 and the p values in Tables 5 and 7 indicate the significance of departures from this expected value. Figures 8 and 9 show the histograms

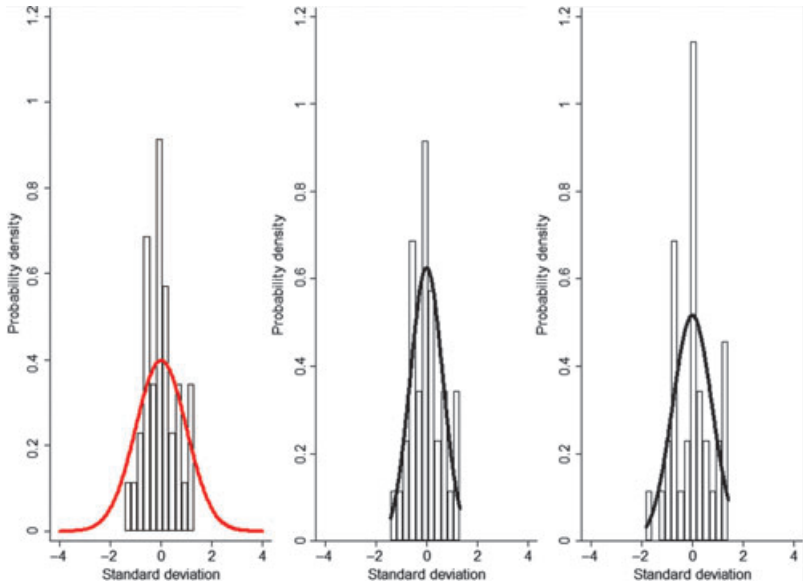

Figure 2 Histograms of reported distributions of the 35 standardised mean differences from Table 3 for seven continuous variables reported in one study of granisetron (reference 90; Appendix S1). The width of each bar is 0.25 SD. The red curve (left graph) is the expected standard normal distribution. The curve generated by the reported distribution (middle graph) was different from the expected, p = 0.0017. After adjustment (right graph), the distribution was not different from the expected, p = 0.06. The point of interest is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the curve).

Table 4 Overall rates of six binomial variables and their distribution for the five groups of a representative study of granisetron by Fujii et al. (reference 90; Appendix S1). Values are number.

			Granisetron dose; μg.kg^{-1}			
	Rate	Placebo (n = 20)	10 (n = 20)	20 (n = 20)	40 (n = 20)	80 (n = 20)
Women	0.4	8	7	8	9	8
Motion sickness	0.09	2	1	2	2	2
Previous PONV	0.02	0	1	0	1	0
Operation two*	0.12	2	3	2	2	3
Operation three*	0.11	2	2	3	2	2
No analgesia	0.37	7	8	7	7	8

*Referring to different operations.
PONV, postoperative nausea and vomiting.

of two categorical variables. Tables 6, 8 and 9 list the p values for the distributions of these and nine other categorical variables.

Figure 10 shows the expected and reported rates of headache in RCT groups authored by Fujii et al. and by others. The former studies had a distribution of headache that was strikingly different from the expected binomial distribution ($p = 1.4 \times 10^{-11}$), whereas the distribution of headache in studies by authors other than Fujii et al. was not different from the expected (p = 0.81). The distributions of weight, age and height in RCTs by other authors were consistent with the expected, in contrast to the distributions in RCTs authored by Fujii et al. (Table 10).

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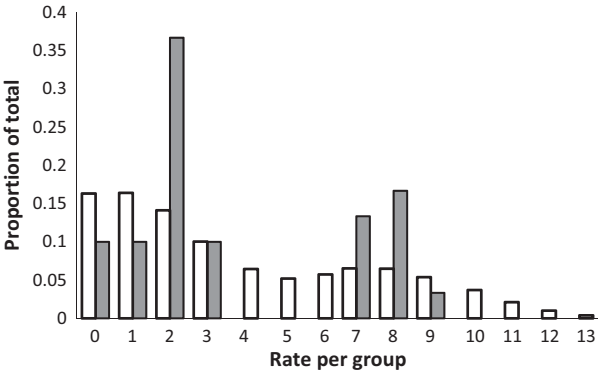

Figure 3 Histograms of reported (■) and expected (by chance; □) distributions of 30 rates (Table 4), summed for six binomial variables reported in a representative study of granisetron (reference 90; Appendix S1). For instance, in Table 4, 11/30 groups reported a rate of 2, which is a proportion of 0.37 on the vertical scale. The reported distribution was not different from the expected distribution, p = 0.13.

Summary of animal studies

Table 11 lists nine continuous variables reported in 26 canine RCTs. The adjusted p values indicate that the distributions are significantly different from that expected for all but one variable, pulmonary capillary wedge pressure; the histograms of the expected and reported distributions for the latter and a representative significantly different variable, transdiaphragmatic pressure at 100 Hz, are shown in Fig. 11.

Individual studies

The preceding analyses combined results from RCTs. I also assessed in isolation each RCT, combining the standardised mean differences for different variables within a study, for instance age, height and weight. Of 142 human RCTs by Fujii et al., 135 (95%) reported mean and SD for at least two continuous variables. Figure 12a shows the p values that the reported

Table 5 Number of reported means for six pre-operative continuous variables in 142 human studies by Fujii et al. (study numbers refer to Appendix S1). The adjusted p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting means with SDs	Standardised SD of means	p value	Studies
Weight	438	0.551	$< 10^{-33}$	1–59, 61–66, 68–73, 75–97, 101–23, 151–69
Age	414	0.567	$< 10^{-33}$	1–17, 19, 21, 24–5, 27–36, 38, 40–6, 48–59, 61–6, 68–73, 75–8, 80–97, 99, 101–3, 105–23, 151–69
Height	447	0.620	$< 10^{-33}$	1–59, 61–66, 68–73, 75–8, 80–97, 99, 101–23, 151–69
LMP	56	0.261	2.22×10^{-16}	37, 42, 47, 50–1, 55–7, 68, 72–3, 81–3, 86, 88, 90, 165
Baseline BP	27	0.363	2.4×10^{-6}	44, 95–7, 105, 107, 115, 151, 153
Gestation	26	0.707	0.036	25, 35, 44, 65, 75, 95–7, 153

BP, blood pressure; LMP, last menstrual period.

Table 6 Number of reported rates for five pre-operative categorical variables in 142 human studies by Fujii et al. (study numbers refer to Appendix S1). The p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting rates	p value	Studies
Previous PONV	83	4.0×10^{-7}	13, 15–8, 22, 27–9, 33, 38–9, 50, 54–5, 57–8, 63, 67–8, 70–1, 80, 90, 92, 95
Motion sickness	88	1.0×10^{-4}	13–8, 22, 27–9, 32–3, 38–9, 50, 54–5, 57–8, 60, 67–8, 70–1, 80, 90, 92, 95
Sex	217	7.1×10^{-3}	1–2, 8, 10–1, 17–9, 21–2, 31, 34, 40–3, 45–6, 49, 52–4, 57–9, 61–4, 66–70, 72–3, 77–8, 80, 82, 85, 87–8, 90–1, 99, 101–12, 114–21, 123, 169
Antihypertensive drugs	73	0.04	105–7, 109, 115, 119
Previous caesarean section	18	0.08	25, 35, 46, 95–7

PONV, postoperative nausea and vomiting.

Table 7 Number of reported means for seven intra-operative continuous variables in 142 human studies by Fujii et al. (study numbers refer to Appendix S1). The adjusted p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting means with SDs	Standardised SD of means	p value	Studies
Operation time	320	0.447	$< 10^{-33}$	1–30, 32–3, 35–45, 47, 49–59, 61–5, 68–73, 75–8, 80–97, 101, 105–6, 108, 111, 113–4, 119, 152–3, 158, 161–2, 165, 167–8
Anaesthetic time	293	0.466	$< 10^{-33}$	1–19, 21–4, 26–30, 32–3, 36–43, 45, 47, 49–59, 61–5, 68–72, 75–8, 80–94, 105–6, 108, 111, 113–4, 119, 152, 158, 161–2, 165, 167–8
Fentanyl	62	0.398	1.6×10^{-9}	57, 65, 71, 73, 75, 80–5, 90, 96–7, 153, 158, 161–2, 165, 167–8
Operative blood loss	32	0.252	1.8×10^{-10}	12, 16, 20, 29, 36, 69, 76, 92, 105, 119
Propofol	63	0.511	1.3×10^{-8}	64–5, 95, 120–1, 123, 154–7, 159–60, 163–4, 166, 169
Paracetamol	19	0.392	2.3×10^{-3}	2, 8, 10–2, 19, 31
Time uterus out	18	0.875	0.03	25, 35, 44, 95–7, 153

Table 8 Number of reported rates for two intra-operative categorical variables in 142 human studies by Fujii et al. (study numbers refer to Appendix S1). The p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting rates	p value	Studies
Uterus exteriorised	18	0.23	25, 35, 44, 95–7
Tubal ligation	18	0.79	25, 35, 44, 95–7

distributions of group means were consistent with the expected distributions in human and animal studies by Fujii et al. The results for other authors are shown in Fig 12b. In the studies by Fujii et al., the distributions were abnormal in 97/135 human RCTs and 22/24 animal RCTs, while distributions were abnormal in 12/139 human RCTs by other authors. A summary of the distribution of adjusted p values for RCTs by Fujii et al. is shown in Table 12. There were insufficient binomial data in any study, human or animal, to generate expected distributions reliably and compare them with reported binomial distributions.

All the continuous variables reported above are combined in Fig. 13, with Fig. 13a displaying 2556 values from RCTs by Fujii et al. (graphs on the left) and 2015 values from other RCTs (graphs on the right). The striking feature is the greater clustering of the data from Fujii, which applies to some extent even to Fujii's trials that do not themselves show distributions different from the expected (Fig. 13b) as well as to those that do show distributions different from expected (Fig. 13c).

The random sampling of eight values from studies by Fujii et al. generates a statistically abnormal distribution whilst an abnormal distribution is only generated after 500 values have been sampled from other RCTs. If these data are combined sequentially, from least to most different from the expected distributions, values from Fujii et al. generate an abnormal distribution after 50 values are analysed and other RCTs generate an abnormal distribution after 333 values are analysed

Table 9 Number of reported rates for four postoperative categorical variables in 142 human studies by Fujii et al. (study numbers refer to Appendix S1). The p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting rates	p value	Studies
Headache	170	1.4×10^{-11}	1–2, 6–16, 21, 24–9, 32, 36, 40–6, 48, 51–2, 54–5, 58–9, 68, 70, 73, 88, 91
Dizziness	117	6.2×10^{-7}	1, 6–7, 9, 12–6, 24–9, 32, 36, 42, 44, 48, 51, 54–5, 58, 68, 70, 76
Drowsiness	201	2.6×10^{-5}	1–2, 6–12, 16, 21, 25, 29, 36, 40–3, 46, 48, 51, 58, 64, 70, 76
Constipation	26	0.08	40–1, 43, 47, 52, 59, 76

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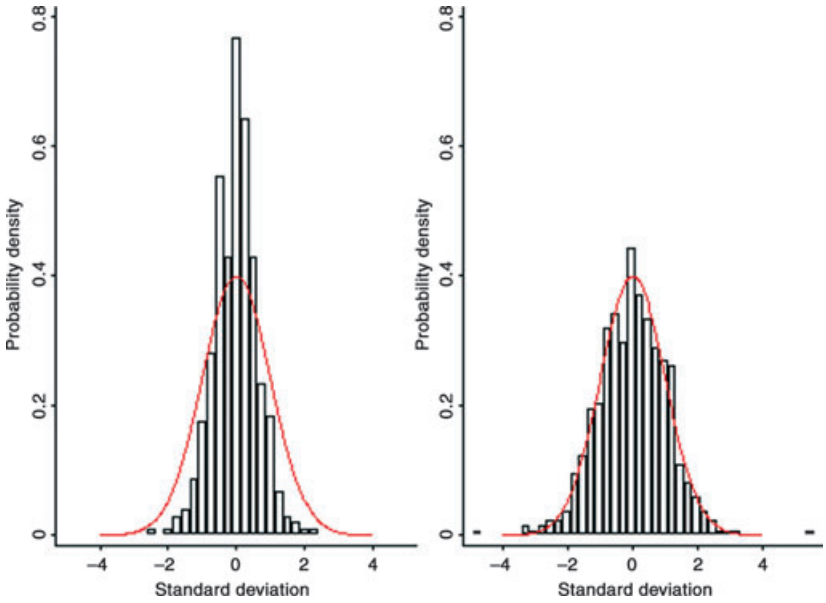

Figure 4 Histograms of mean age distributions reported by Fujii et al. (left) and by others (right). The distribution reported by Fujii et al. was different from the expected, $p < 10^{-33}$, whilst that reported by others was not, $p = 0.132$. The width of each bar is 0.25 SD. The red lines are the respective expected standard normal distribution. The point of interest in the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

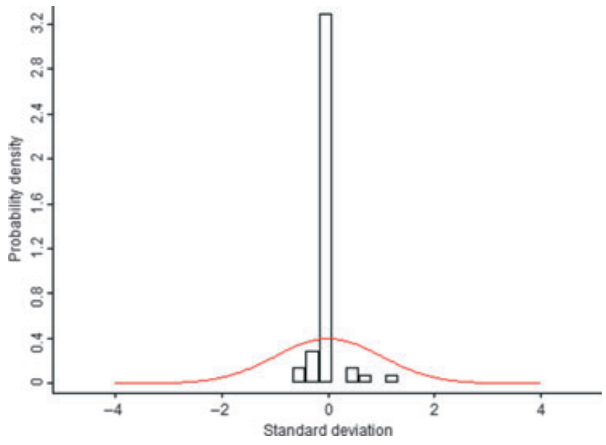

Figure 5 Histogram of 56 standardised mean differences for last menstrual period from 18 human trials by Fujii et al. (Appendix S1; references from the same studies as in Table 5). The reported distribution was different from the expected, $p = 2.22 \times 10^{-16}$. The width of each bar is 0.25 SD. The red line is the expected standard normal distribution. The point of interest in the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

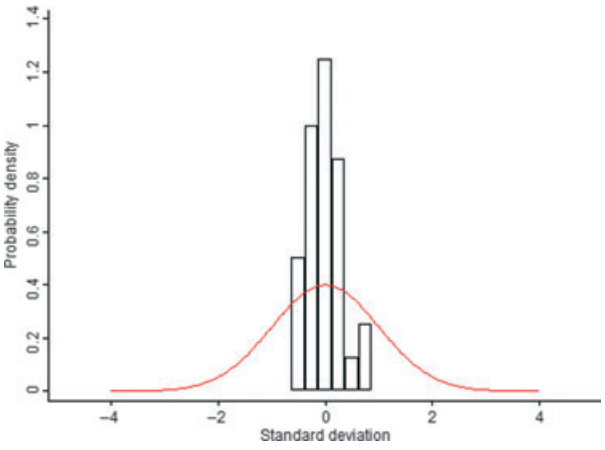

Figure 6 Histogram of 32 standardised mean differences for blood loss from 10 human trials (Appendix S1; references from same studies as in Table 7). The reported distribution was different from the expected, $p = 1.8 \times 10^{-10}$. The width of each bar is 0.25 SD. The red line is the expected standard normal distribution. The point of interest in the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

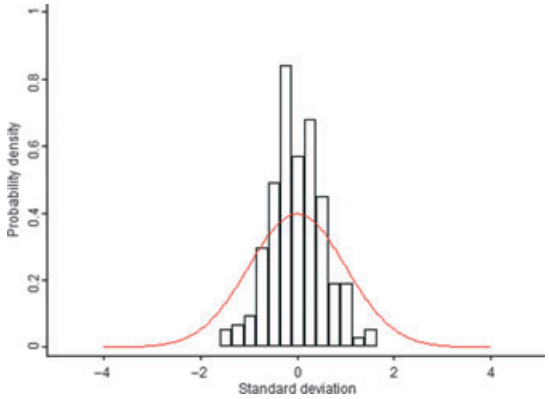

Figure 7 Histogram of 293 standardised mean differences for anaesthetic time from 94 human trials (Appendix S1; references from same studies as in Table 7). The reported distribution was different from the expected, $p < 10^{-33}$. The width of each bar is 0.25 SD. The red line is the expected standard normal distribution. The point of interest in the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

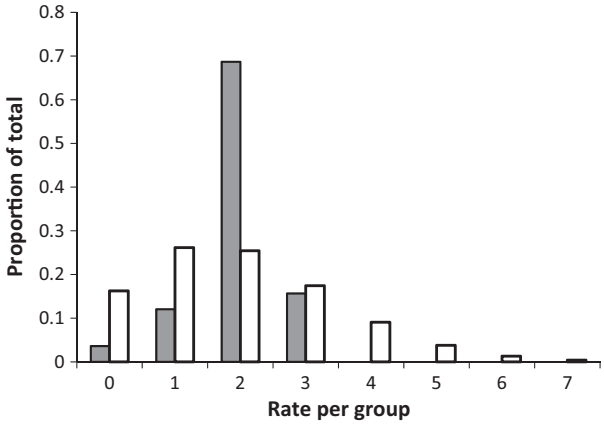

Figure 8 Histograms of the reported (■) and expected (by chance; □) distributions for 83 rates of previous postoperative nausea and vomiting from 26 human trials (Appendix S1; references the same as the studies in Table 6). The reported distribution was different from the expected, $p = 4.0 \times 10^{-7}$. The point of interest is the narrower width of the distribution of reported data and the height of the bars in the centre of the distribution (that suggests clustering) of the reported data vs the expected.

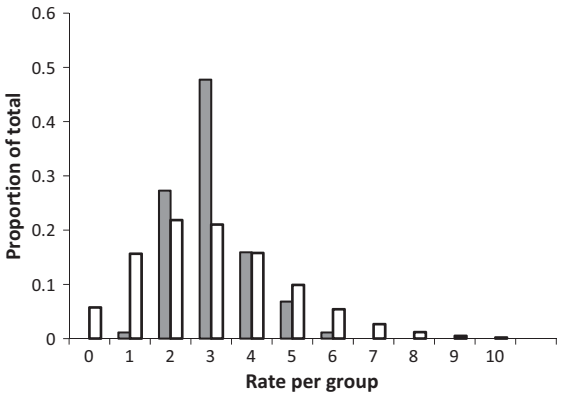

Figure 9 Histograms of the reported (■) and expected (by chance; □) distributions for 88 rates of motion sickness from 28 human trials (Appendix S1; references the same as the studies in Table 6). The reported distribution was different from the expected, $p = 1.0 \times 10^{-4}$. The point of interest is the narrower width of the distribution of reported data and the height of the bars at the centre of the distribution (that suggests clustering) of the reported data vs expected.

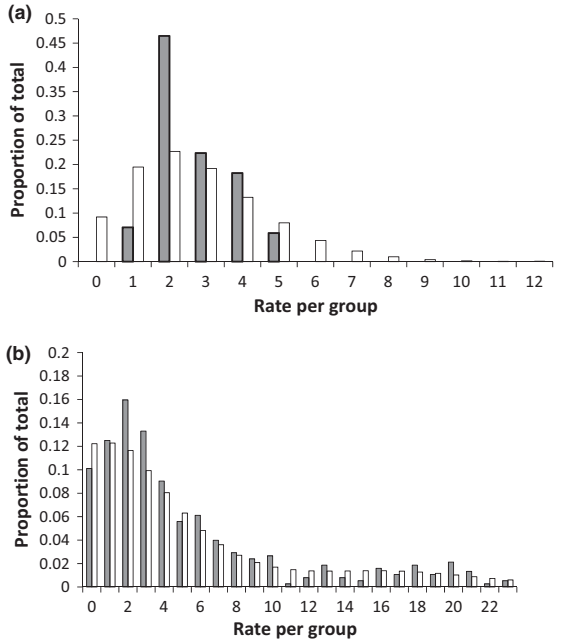

Figure 10 Histograms of the reported (■) and expected (by chance; □) distributions for headache in studies of postoperative nausea and vomiting by (a) Fujii et al. (Appendix S1; available online; references the same as the studies in Table 9) and (b) other authors (Appendix S1; references 1–126). The reported distribution was different from the expected for studies by Fujii et al. ($p = 1.4 \times 10^{-11}$), but was not different for those by other authors, $p = 0.81$.

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Table 10 Number of reported rates for three postoperative categorical variables in 142 human studies by Fujii et al. and 145 other RCTs. The adjusted p value quantifies the chance that the reported distribution was consistent with the expected distribution, which was unlikely for weight, age and height in RCTs by Fujii et al. Appendix S6 is available online.

Variable	Authors	Groups reporting rates	Standardised SD of means	p value	Studies
Weight	Fujii et al.	438	0.551	$< 10^{-33}$	See Table 5
Weight	Other authors	359	1.06	0.13	See Appendix S6
Age	Fujii et al.	414	0.567	$< 10^{-33}$	See Table 5
Age	Other authors	556	1.04	0.14	See Appendix S6
Height	Fujii et al.	447	0.620	$< 10^{-33}$	See Table 5
Height	Other authors	146	0.93	0.24	See Appendix S6

Table 11 Number of reported means for nine continuous variables in 26 canine studies by Fujii et al. (study numbers refer to Appendix S1). The adjusted p value quantifies the chance that the reported distribution was consistent with the expected distribution.

	Groups reporting means with SDs	Standardised SD of means (expected 1)	p value	Studies
Right atrial pressure	87	0	$< 10^{-33}$	124, 126–8, 130–2, 140–1, 147–6
Transdiaphragmatic pressure at 100 Hz stimulation	118	0.203	$< 10^{-33}$	124–137, 140–1, 144–6, 148–9
Pulmonary artery occlusion pressure	56	0.351	$< 10^{-33}$	127–9, 131–2, 143, 145–6
Heart rate	108	0.330	1.6×10^{-11}	124–137, 140–1, 143–8
Transdiaphragmatic pressure at 20 Hz stimulation	77	0.178	$< 10^{-33}$	124–137, 140–1, 144–6, 148–9
Mean pulmonary arterial pressure	69	0.389	4.6×10^{-15}	126–8, 130–2, 140–1, 143, 145–7
Mean arterial pressure	107	0.482	1.6×10^{-8}	124–141, 143–8
Cardiac output	62	0.511	9.5×10^{-3}	126–8, 130–2, 138, 143, 145–6
Pulmonary capillary wedge pressure	18	0.775	0.42	126, 140–1

(thick black and red lines, respectively, in Fig. 14). Artificially increasing the variance by 9% of the 1520 values from RCTs of authors other than Fujii resulted in a cumulative distribution that was as expected (making the line in Fig. 14 horizontal; not shown). This suggested that a degree of clustering was likely when combining different trials (see Discussion); however, adjustment little affected Fujii's data.

Discussion

There is no 'correct' or singular statistical method to detect if data follow highly unusual distributions. Using the methods I have employed, my main conclusion is that the distribution of variables reported by Fujii et al. in the trials analysed varied less than expected by chance. Scientific notation might not convey how unlikely it is that natural processes could account for these distributions. In Table 7, for example, a p value of $< 10^{-33}$ is a probability of fewer than one in a decillion (or 1 in 1 000 000 000 000 000 000 000 000 000 000 000), the chance of selecting one particular atom from all the human bodies on earth. It is also striking that when the results of several trials are combined, the reported distributions for Fujii increasingly depart from the expected, whereas those for other authors do so relatively little (and can be corrected by modest adjustment; Fig. 14).

In my analysis, I did not impose any external theoretical distribution upon the data that was not already a necessary consequence of the data embedded within these RCTs. The single assumption common to calculating the expected variation, for both continuous and categorical variables, was that the study groups represented subjects sampled randomly from the same population. A well-designed RCT should ensure random distribution of variables measured before intervention, including age, weight, height, sex, chronic medications, a history of PONV or motion sickness, LMP and

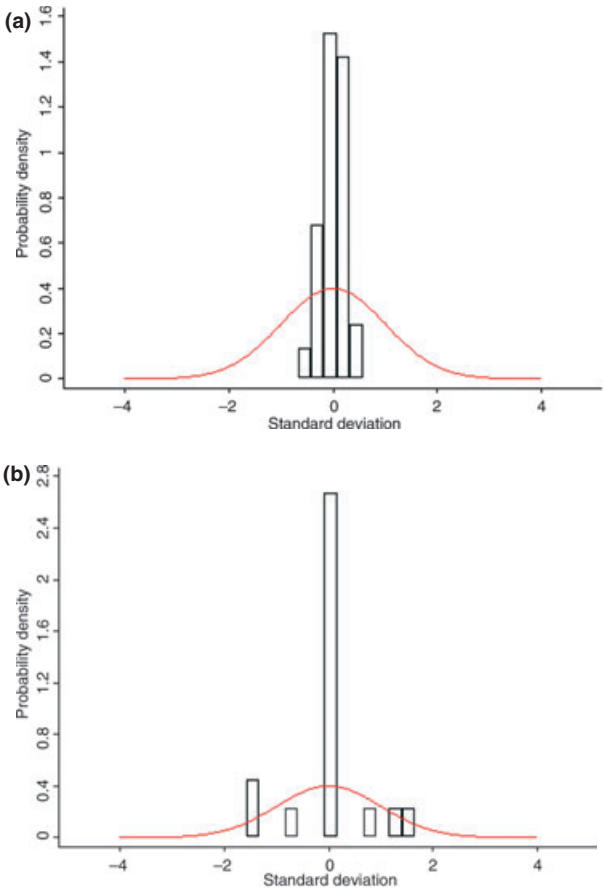

Figure 11 Histograms of the distributions of standardised mean differences for two continuous variables in canine studies by Fujii et al.: (a) transdiaphragmatic pressure at 100 Hz stimulation, $p < 10^{-33}$ (Appendix S1; references 124–137, 140–1, 144–6 and 148–9); and (b) pulmonary capillary wedge pressure, p = 0.42 (Appendix S1; references 126 and 140–1). The width of each bar is 0.25 SD. The red line is the expected standard normal distribution. The point of interest in the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

gestation. However, *after* the groups have been exposed to allocated interventions – placebo, drugs and so on – one cannot assume that the distribution of the data from the groups will be the same. One might therefore conclude that comparison of reported vs theoretical distributions is invalid for some of the variables reported here, including side effects such as drowsiness, dizziness and headache, the last of which aroused Kranke et al.'s suspicion [1]. For instance, a group given granisetron might report more headaches than a group given saline. One does not know whether these different rates represent chance variation (sampling from a single population rate) or an effect of granisetron (sampling from two different population rates). One therefore does not know what distribution to expect. However, not only were the rates of these side effects reported by Fujii et al. consistent with sampling from a single population, they were so invariant that they were inconsistent with the variation one would expect to arise by chance.

There are two types of probabilities that one can calculate for the distributions of binomial characteristics: (i) the probability of observing a particular rate of occurrence of an event; and (ii) the probability that a particular rate is consistent with the expected rate. Kranke et al. calculated the first type of probability, whereas I have calculated the second type. The problem with calculating the first, the probability of a specific rate, is interpreting what it means – because any single rate is very unlikely. For example, when rolling two dice, the chance of throwing a 5 and a 2 is exactly the same as the chance of throwing any other combination of two numbers; but the chance of throwing a total of 7 is higher (18%) than for other sums (because it can be attained by more combinations than for other totals), hence the need to study 'distributions' (which, in this analogy, would be the respective incidences of the sum of two dice-throws from 2 to 12) rather than just 'chance of occurrence'. As with rolling dice, the single most likely distribution of 18/270 headaches in one group of 45 women is 3/45, a probability of 0.23, or 1 in 4. Fujii et al. reported this rate in 6/6 groups (reference 1; Appendix S1); the probability of obtaining this precise distribution in this study is 0.23^6, or 1 in 6800. Kranke et al. combined such probabilities across 18 RCTs to estimate a 1 in 147 million chance that 10 of them would report the same headache rate in all groups. However, the starting point for this calculation was that there is something special about equal rates of headache in all groups. A homogenous distribution (such as 3/45 people having headache in all six groups) is not the most likely distribution but it is also not the least likely, which would be all 18 headaches in one group. Indeed, six groups each with 3/45 headaches is a distribution that has borderline probability, given the expected

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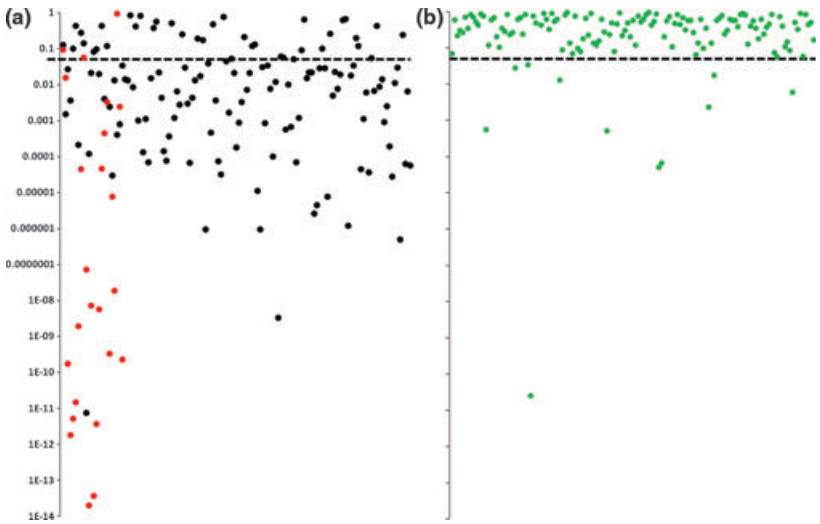

Figure 12 Plot of p values that the reported distribution was consistent with the expected distribution (adjusted). The p values (*y*-axis, log scale) are for (a): Fujii's human RCTs (●) and animal RCTs (●) and (b): the RCTs of other authors (●). The horizontal grey dotted line represents p = 0.05. The point of interest is that whereas only 12 trials from other authors have p values strikingly less than p < 0.05 (panel (b), below the horizontal dotted line), a very large number of Fujii studies do so (including the majority of animal studies).

Table 12 Distributions of adjusted p values arising from testing the null hypothesis that the variance of continuous variable means in individual randomised controlled trials by Fujii et al. (that reported mean and SD for at least two continuous variables) was as expected (sdtest; see Appendix A). Values are number (proportion).

	p < 0.00001	p < 0.001	p < 0.01	p < 0.05	p > 0.049
Human studies (n = 135)	9 (7%)	30 (22%)	27 (20%)	31 (23%)	38 (28%)
Animal studies (n = 24)	15 (62%)	3 (13%)	2 (8%)	1 (4%)	3 (13%)

p values from individual studies are shown in Fig. 12a.

distribution for this study (p is around 0.05, or 1 in 20). A likelihood of 1 in 147 million probably underestimates the chance of 10/18 RCTs' reporting the same rates in all groups, whereas the value I calculated for all the distributions in these 18 RCTs, of 1 in 5650, might well overestimate the chance of this distribution. I calculated the expected rate of a binomial variable from the observed rate. This mathematically couples the expected distribution to the observed distribution, making the comparison less likely to identify differences. In such a conservative analysis, any significant result therefore more robustly implies substantial disparity between the expected and reported distributions. Fujii et al. continued to publish RCTs that included headache rates after Kranke et al.'s letter was published [1]. In addition, I calculated the probability of any reported distribution occurring, rather than limiting the analysis to homogenous distributions. The final probability that the difference between the reported and expected distributions arose by chance was 1 in 71 billion (Table 9).

I have previously mentioned that a graph of sample means will cluster around the population mean, shaped in a normal curve. Two characteristics of the samples determine the width or spread of this curve: the sample size and the variability of the measurements. Less variable measurements (smaller standard deviation) and more measurements will result in less variable means that, in turn, populate a narrower graph of means. The standard deviation in a sample and the sample size should make the calculated width of this

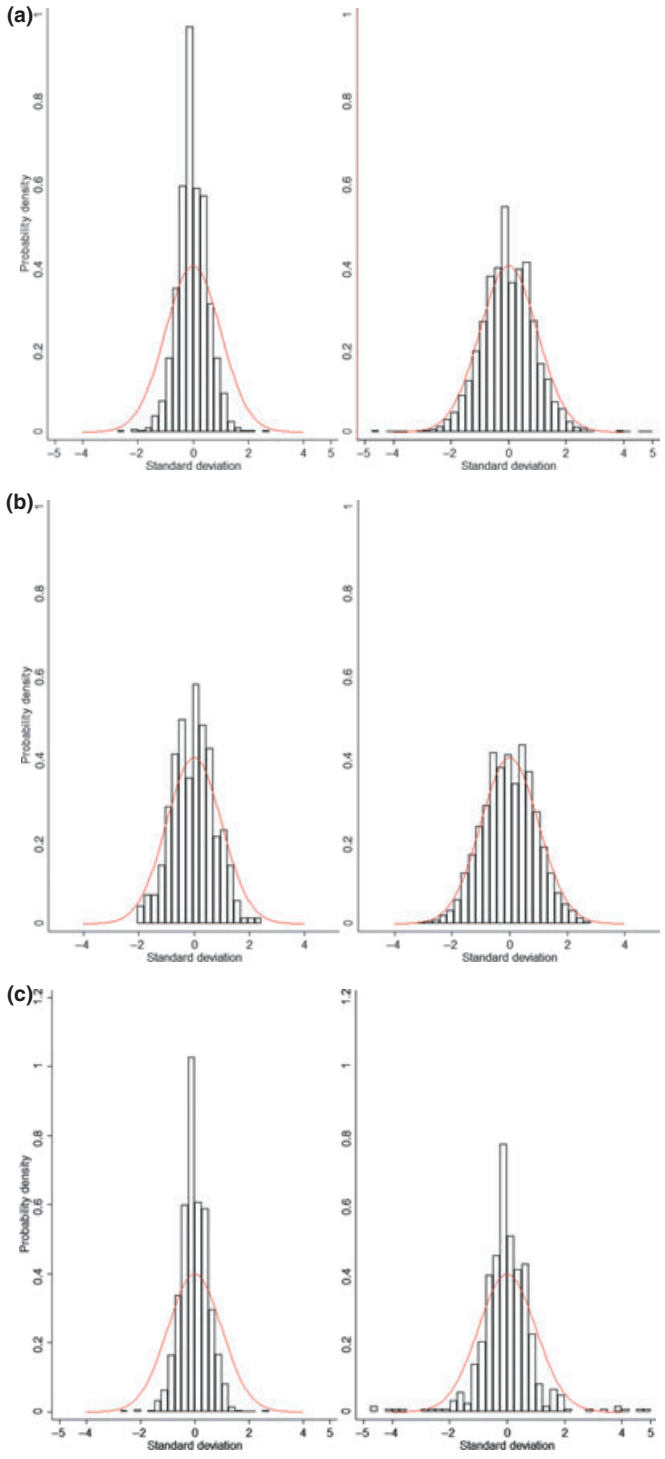

Figure 13 Histograms of the distributions of standardised mean differences for RCTs by Fujii et al. (left) and by others (right): (a) including values from all RCTs (2556 by Fujii et al., 2015 by others); (b) including values from only those RCTs that demonstrated the least aberrant distributions (284 by Fujii et al., 1520 by others); (c) including values only from those RCTs with the most aberrant distributions (2272 by Fujii et al., 495 by others). The width of each bar is 0.25 SD. The red line is the expected standard normal distribution. The point of interest in all the Fujii studies is the abundance of standardised mean differences around zero (above the red curve) and their paucity to either side (i.e. the bars on either side do not extend along the *x*-axis to meet the limits of the red curve).

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【資料 1 - 18】

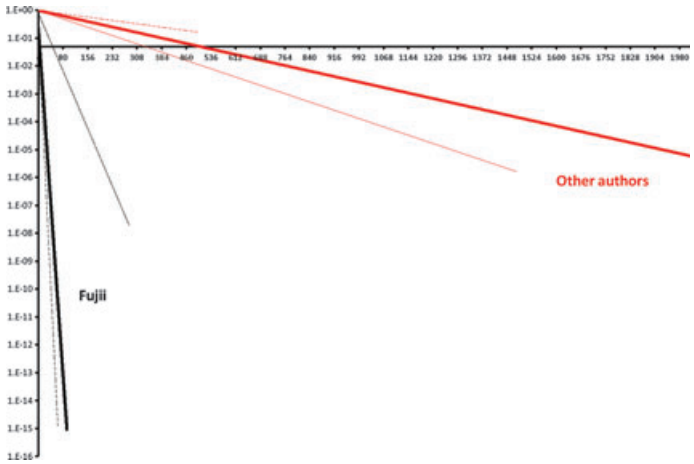

Figure 14 Decreasing probabilities of the reported distributions occurring by chance as more continuous data are analysed. The horizontal axis is the number of standardised mean differences analysed. The vertical axis (exponential scale) is the probability that the analysed distribution is consistent with the expected, where 1.E-02 is 1×10^{-2} or 1 in 100. Black lines are generated from RCTs reported by Fujii et al., red lines are for other RCTs. Thick lines are from all human RCTs (corresponding to Fig. 13a), thin lines are using values from RCTs with the least aberrant distributions (corresponding to Fig. 13b) and broken lines are using values from RCTs with the most aberrant distributions (corresponding to Fig. 13c). The thick and dotted black lines for Fujii et al. have been curtailed and actually extend to a value of $< 1 \times 10^{-600}$.

graph, or SEM, inextricably linked with the spread of the reported means. Just as Fujii et al.'s group rates for binomial variables clustered around the population rate, so too did their group means cluster abnormally tightly around the population mean. However, it is important to recognise that if the mean values are reported insufficiently precisely, artefact may be introduced, itself causing the reported distribution of means to cluster more tightly around the population mean than expected. This is most clearly demonstrated when the SEM calculated for each group is smaller than the precision to which the mean is reported, for instance, if mean height is reported to the nearest centimetre and the SEM is reported as 0.3 cm. In Fujii et al.'s data, the only human continuous variable reported for which this problem increased clustering during analysis was last LMP (Fig. 5). This problem was of particular concern for 46 of 56 groups in which the mean LMP was reported to the nearest day (mean (SEM) 16 (0.52) days in all groups). If means between 15.1 and 16.9 in these 46 groups were rounded up and reported as 16, one would have expected 2/46 means to have been $\leq$ 15 days and 2/46 to have been $\geq$ 17 days; if mean LMPs > 16.5 were rounded up to 17 and those < 15.5 were rounded down to 15, one would have expected about 8/46 means to have been $\leq$ 15 days and 8/46 to have been $\geq$ 17 days. In the first scenario, reporting 46 out of 46 means as 16 days has a probability of 0.17 of occurring by chance and in the second scenario, a probability of 2.5×10^{-6}, 1 in 400 000.

Reported LMP might also cluster because of women's preference to report particular values. However, this cannot explain the results in the animal studies. In RCTs of dog diaphragmatic function, the mean value for right atrial pressure (RAP) in all 87 groups was 5 mmHg. With an average SEM of 0.56 mmHg, one would have expected some RAPs to be 4 or 6. If any RAP mean between 4.1 and 5.9 mmHg was reported as 5 mmHg, one would have expected 9/87 means to have been either 4 or 6 mmHg. If mean RAPs > 5.5 mmHg were rounded up to 6 mmHg, and those < 4.5 mmHg were rounded down to 4 mmHg, one would have expected 32/87 means to have been 4 or 6 mmHg. The probabilities that 87 of 87 means would be 5 mmHg are 1 in 300 in the first scenario and 1 in 72 billion in the second scenario.

The combination of values from RCTs that individually had distributions close to the expected led to abnormal clustering after 50 Fujii values and after 333 values from other RCTs (Fig. 14). This finding might be

because there was something wrong with the values or something wrong with the analysis, or both. Multiplication by 1.09 of the 1520 values from 117 other RCTs with the least aberrant distributions increased their variance and prevented this clustering, whilst multiplication by 1.30 was needed to normalise the 285 values from the 19 Fujii RCTs with the least aberrant distributions. Summation of values (both from Fujii's and other authors' trials) might be revealing aberrant distributions that remain undetected when RCTs are analysed individually, in much the same way that a meta-analysis can identify an effect that is undetected by single underpowered RCTs. By far the majority of RCTs by Fujii et al. remain aberrant despite attempts to correct them and the overall steepness of the lines in Fig. 14 provide a statistical index of suspicion that the data are aberrant.

It is usual to modify or correct analyses of means, medians or rates when tests are not independent. In this paper, there are two sources of correlated variables: those that are biologically associated, such as age, sex, height and weight; and those that are constrained by another analysed variable, such as surgical times being necessarily less than anaesthetic time. I have adjusted the analyses for continuous variables in this paper, but not as a consequence of this concern. The analyses of categorical data were conservative for the reasons I have stated, therefore I did not adjust these further.

In conclusion, I have shown that the distributions of continuous and categorical variables reported in Fujii's papers, both human and animal, are extremely unlikely to have arisen by chance and if so, in many cases with likelihoods that are infinitesimally small. Whether the raw data from any of these studies can be analysed, and whether this might provide an innocent explanation of such results [4], is beyond the scope of this paper. Until such a time that these results can be explained, it is essential that all Fujii et al.'s data are excluded from meta-analyses or reviews of the relevant fields. The techniques explored in this paper offer a method of assessing data integrity in RCTs published by other authors, for instance within systematic reviews by the Cochrane Collaboration.

Competing interests

No external funding and no competing interests declared.

Acknowledgements

I am indebted to Professor Jaideep J Pandit and Dr Steve Yentis for their encouragement, support and help. This paper has benefitted from their advice. Much of the clarity this paper possesses has been generated by their hard work, whilst the obscurity that remains is mine alone.

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Appendix A
Method of generation of expected categorical and continuous distributions and their subsequent statistical analysis

I have generalised the analysis of binomial variables, from the specific assessment of equal incidences in study groups to a general comparison of the expected incidences with reported incidences. I have also analysed the distribution of continuous variables, such as height. The central limit theorem applies to the mean values of samples taken repeatedly from the same population. The mean sample values ($\bar{m}$) consequently follow a normal distribution around the mean of the population μ from which the samples were taken. Subtraction of the sample means from the population mean will produce a normal curve of values with a mean of zero. The standard deviation (SD) of this curve is estimated by the SEM of the samples used to construct the curve. The SEM is calculated from the SD of any of the sample SDs and the size of the sample (n):

$$\mathrm{SEM} = \mathrm{SD}/\sqrt{\mathrm{n}}$$

Division of ($\bar{m}$ − μ) by the SEM will standardise the normal curve so that the distribution of reported mean differences will remain centred on zero, but the SD of the curve should equal one. For example,

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Table 13 Method of calculation.

Variable	Group 1 (n = 24)	Group 2 (n = 23)	Group 3 (n = 23)	Mean
Mean $\bar{m}$	121.1	119.9	117.8	119.6 (μ)
SD	11.5	11.1	10.1	10.9
SEM	2.35	2.31	2.11	2.26
$\bar{m}-\mu$	1.5	0.3	−1.8	0
$(\bar{m}-\mu)/SEM$	0.66	0.13	−0.79	0
Adjusted*	0.72	0.14	−0.86	0

*For the analysis of means in individual RCTs, I increased the variance of the standardised mean differences by an arbitrary factor determined by the standard deviation of the calculated SEMs (SD_{SEM}), divided by the square root of the mean SEM; $(\bar{m}-\mu)/SEM \times (1 + (SD_{SEM}/\sqrt{SEM}))$. In the Table, the standard deviation of the three SEMs (2.35, 2.31, 2.11) is 0.129. The square root of the mean SEM (2.26) is 1.5. Therefore, the adjustment factor is 1 + (0.129/1.5), or 1.086.

Table 13 shows mean (SD) height (in cm) reported in three groups (Appendix 1, reference 2), with calculations of the SEM and standardised mean differences, $(\bar{m} - \mu)/SEM$.

I generated expected binomial distributions in Excel® (v 2007, Microsoft Corp., Redmond, WA, USA).

$$= IF(a > n, 0, BINOMDIST(a, n, p, FALSE)),$$

where a is an integer; n is the number of successes in each group; p is the probability of success (the proportion of participants allocated to the different groups that had a success); FALSE instructs the program not to generate the cumulative probability distribution.

Unlike Kranke et al., I calculated a separate population rate probability 'p' for each RCT rather than assuming that there was a common underlying rate across RCTs. I combined the expected distributions from different studies and compared the summed distribution with that reported.

I used Intercooled STATA® 12 (StataCorp LP, College Station, TX, USA) to test whether the reported-to-expected categorical distributions (Fisher's exact test), and the variances of reported-to-expected standardised distributions, significantly departed from those which would arise from chance (sdtest).

Supporting information

Additional Supporting information may be found with the online version of this article:

Appendix S1 Randomised controlled trials authored by Fujii and colleagues, identified from a literature search between 1991 and July 2011.

Appendix S2 Randomised controlled trials of postoperative nausea and vomiting prophylaxis reporting headache, not authored by Fujii, identified from a literature search between 1991 and July 2011.

Appendix S3 Thirty-one references for RCTs of granisetron, authors other than Fujii.

Appendix S4 One hundred references for RCTs by authors other than Fujii reporting rates of nausea and vomiting with rescue for droperidol, granisetron and metoclopramide.

Appendix S5 Sixty-five references for RCTs by authors other than Fujii reporting rates of side effects in studies of PONV prevention.

Appendix S6 References for weight, age and height in RCTs by authors other than Fujii et al.

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Editorial

On statistical methods to test if sampling in trials is genuinely random

"Man is an orderly animal. He finds it very hard to imitate the disorder of nature." [1].

Humans are not good at identifying randomness: our minds naturally look for patterns, even when there are none. Furthermore, we are poor at creating random data. Famously, as a result of listener complaints, the first iPod 'shuffle function' had to be changed to make it less random, but appear more random to the human ear (see http://electronics.howstuffworks.com/ipod-shuffle2.htm).

Random sampling in research (e.g. by computer- rather than human-generated random numbers) importantly reduces the potential for bias. In this issue of *Anaesthesia*, Carlisle offers persuasive evidence that the sampling upon which the results of Fujii's many published trials are based are so unlikely to arise from chance, that it is appropriate to disregard them from further scientific consideration [2]. The purpose of this commentary is to try to simplify Carlisle's rigorous analysis so that readers might more easily follow his arguments.

Is a coin or set of dice fair?

"…it raises in a sharp and concrete way the question of what is meant by randomness, a question which, I believe, has not been fully worked out." [1].

Carlisle was fundamentally interested in the 'fairness' of the sampling used in Fujii's data. The mathematics evolved from the 16th century, from an interest in gambling where the fundamental question was: are the dice/coins/cards fair? Cardano formally investigated the statistics of gambling in his book *Liber de Ludo Aleae*, and the analysis was continued by Pascal and Fermat, in a famous correspondence that began when advising a mutual gambling friend [3].

Anaesthetists are quite used to statistical testing where, say, two groups are subjected to two different interventions (one of which may be control), and an outcome (e.g. blood pressure (BP)) is assessed using a t-test or nonparametric equivalent to generate a p value. Simply, this indicates the likelihood that the observed BP differences could have arisen from chance; i.e. $p < 0.05$ implies that the observed difference has a 5% probability or less of arising by chance (conventionally regarded as 'significant').

However, Carlisle was *not* interested in this sort of comparison. Rather than assess differences between Fujii's test and control data, or between Fujii's data and the results of other workers, Carlisle instead asked a more subtle question: if we confine our analysis solely to data within Fujii's samples (and particularly the control samples), how likely is it that their reported distributions could have arisen by chance? (Separately within the paper he also asked this of other authors). For example, were the relative proportions of males and females, the incidence of nausea/vomiting, etc, those that would be expected? To answer this entirely different question, Carlisle did not perform a statistical comparison of one experimental dataset versus another but rather, a comparison of the experimental results (in absence of any intervention) with those that *would be expected by chance*.

But how can we predict what chance can produce? We may be tempted to think that any pattern is possible but in fact, chance produces remarkably predictable outcomes in the long run. Carlisle used methods that parallel those described long ago by the biologist JBS Haldane (son of the Oxford physiologist JS Haldane) in two letters to *Nature*, describing his analysis of suspicious data [1, 4, 5]. Haldane, like Carlisle, drew back from an accusation of fraud, but likened the chance to a monkey

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typing out Hamlet by sheer luck. The p values found by Carlisle and Haldane are similar.

There are broadly two types of data in question: categorical, grouped into distinct types (e.g. male/female or headache/no headache); and continuous, having any value within a scale (e.g. BP, in mmHg).

We can try to understand the expected-by-chance distributions of categorical data by using much simpler analogies of tossing coins or throwing dice. For both, the results can only have fixed values of heads/tails or the numbers on the dice, but no value in between. Unsurprisingly, the probability of obtaining a certain value when throwing a single six-sided die is ~16% (Fig. 1) but this is only the *average* expectation. The variance (V), i.e. the degree of departure from expected (or SD, which is $\sqrt{V}$), becomes smaller as the number of throws increases (Fig. 1). This is described by a mathematical function known as the binomial probability distribution (which applies to any case of independent events where there are only two possible outcomes; here, throwing a six on a die vs not throwing a six). If the number of throws is n and the probability of the event is p, then the mean rate (μ) of the event (in this case throwing a six) happening is given by:

$$\mu = n.p \qquad (1)$$

In this case, μ is 16/100 throws, 32/200 throws, etc. The SD of this (which can be proved mathematically for the binomial distribution) is given by:

$$\mathrm{SD} = \sqrt{n\,p(1-p)} \qquad (2)$$

Therefore for 60 throws, the mean (SD) number of sixes should be ~10 (3), for 100 throws it is ~16 (4), for 1000 throws, it will be ~160 (12), and so on. Readers should see that, because we now have a *variance* (or SD), we can use this to assess statistically the departures of any actual data from what is expected (I will not detail the calculations here). Thus if a friend offers a die that results in 30 sixes in 100 throws, we can use statistical testing (using the principles of variation above) to assess its fairness (the actual chance of this is $p < 0.005$; Fig. 1). Incidentally, another approach that can be applied to all the numbers thrown is to use the chi-squared test; this yields the same result.

When throwing *two* dice, the plot of possible totals now resembles something readily recognisable

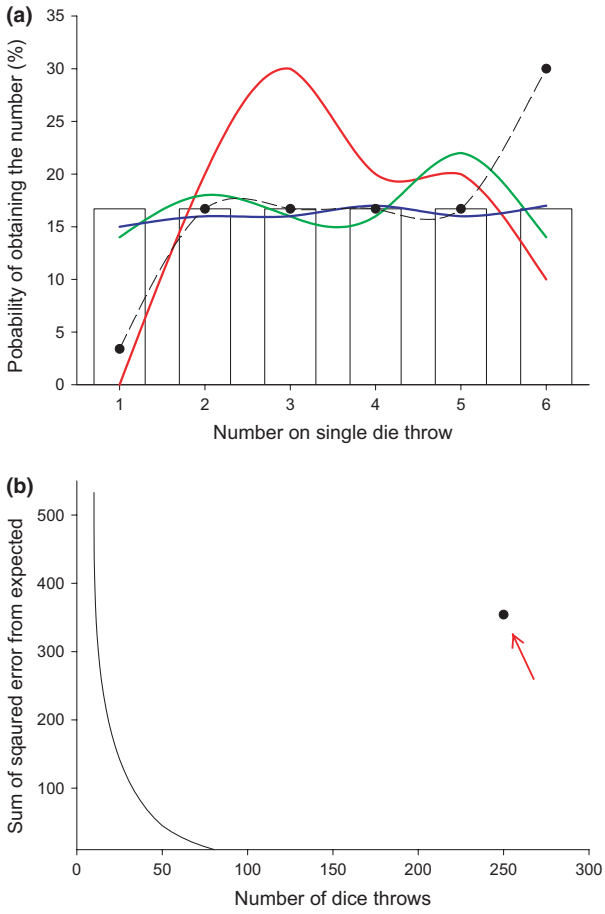

Figure 1 (a) Representation of the average expected probability (bars) of throwing the number (on x-axis) with a single die. The results of simulations throwing a single die 10 (—), 50 (—) and 250 (—) times are plotted (for clarity) as lines, with the dots (– –) representing a slightly loaded die thrown 250 times. (b) Plot of the sum of squared errors for the number of dice throws, showing that with increasing throws, the result gets closer to the expected, becoming a trivial difference after ~50 throws. The single dot (with arrow) shows the sum of squared error for the loaded die (which has a similar sum of squared error as the red line in panel A, but after 250 throws rather than just 10).

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as a normal (Gaussian) distribution for continuous data, with 7 being the most likely total as it arises from most combinations (Fig. 2). If our friend's dice deviate from this overall pattern (Fig. 2), we know exactly how to calculate the probability of that result (this is the basis of the t-test or other tests using variances to compare datasets). Readers might compare the general forms in Fig. 2 with figures 2–10 and 13 in Carlisle's paper [2].

Similar considerations apply with coin throwing. With one coin, the probability of a head (H) or tail (T) is 1:1. With two coins, the ratio of HH, HT, TT is 1:2:1. With three coins, the ratio of 3H, 2HT, 2TH, 3T is 1:3:3:1, and so on. These ratios can be arranged to the pattern commonly known as Pascal's triangle (Fig. 3), which is also obtained by a mathematical function known as the binomial expansion (a term used in Carlisle's paper [2]). This is mathematically related to the binomial probability distribution described above. It is possible to expand any power of $x + y$, denoted $(x + y)^n$, into an expression with a general form (Box 1).

Box 1

$$(x+y)^2 = x^2 + \mathbf{2}xy + y^2 \quad (3)$$

$$(x+y)^3 = {}^3 + \mathbf{3}x^2y + \mathbf{3}xy^2 + y^3 \quad (4)$$

$$(x+y)^4 = x^4 + \mathbf{4}x^3y + \mathbf{6}x^2y^2 + \mathbf{4}xy^3 + y^4 \quad (5)$$

and so on. The coefficients (the bold numbers) form the numbers in Pascal's triangle and are useful as shortcuts in probability calculations. For example, the answer to: 'what is the chance of getting exactly 2 heads with 3 coin tosses?' is obtained by looking at the 3rd row of the triangle, 2nd position along. The sum of numbers (indicating the total possible results (Fig. 3 and Equation 4) is 8, so that chance is 3/8, or ~37.5%. To summarise: binomial probabilities can be described mathematically, in a manner linked to Pascal's triangle, which is in turn a useful shortcut to the calculation of those probabilities.

Superficially, there seems one limitation to applying these examples of coins and dice to real life: we know in advance the precise probability of their average outcomes. How can we know in advance how many headaches there should be in any group of people? The answer is that we don't, but then we don't need to. Instead, we can look for how symptoms like headaches (or other

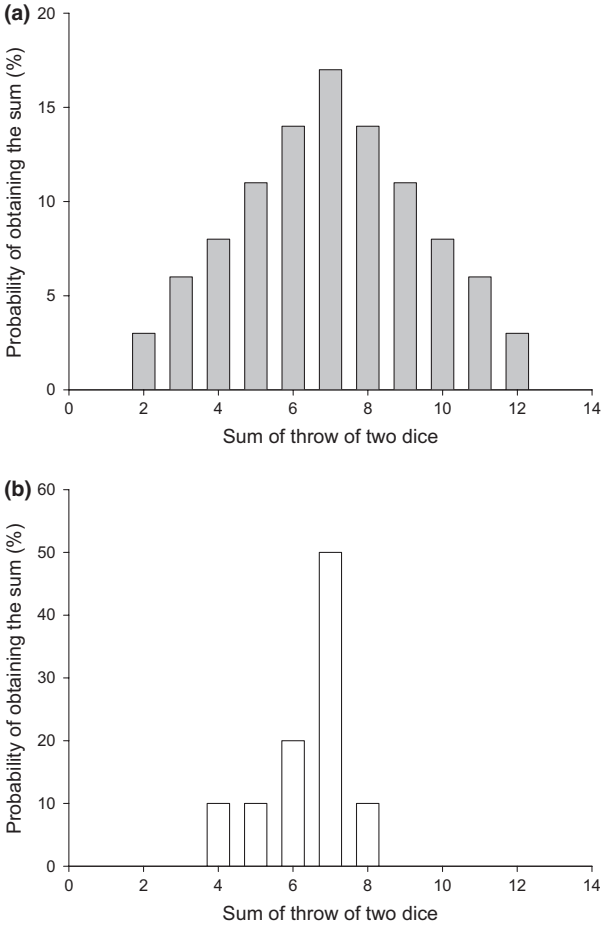

Figure 2 (a) Simulation of the ideal sums of throwing two dice 100 times, resembling a normal (Gaussian) distribution. (b) The simulated sum of throwing a slightly loaded dice 100 times, where only the sums 4–8 appear.

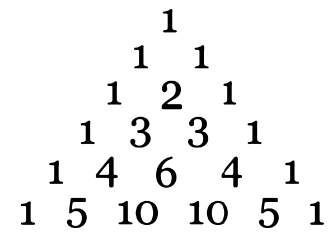

Figure 3 Pascal's triangle. By convention the 1st row (containing only 1) is called row zero.

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binomial factors like sex, etc) are *distributed* across randomly selected groups. If 100 women are randomly divided between two groups, we expect there to be 50 women in each group on average (but not precisely; SD = 5 by Equation 2). If the baseline incidence of headache is 10%, then in a group of 100 people there should be 10 headaches on average (but not exactly; SD = 3 by Equation 2). Therefore, the analyses do, in fact, resemble coin tossing. Reported distributions for such things can then be unusual in two ways. First, because they are *more aberrant* than expected (as in our friend's single slightly-loaded die, Fig. 1) or second, because they are *less variable* than expected (as in the friend's two slightly-loaded dice in Fig. 2). Either way, we can calculate (using the mathematics of binomial distribution) a p value for the difference between actual and expected distributions. In short: if we tried to fabricate a dataset, we would find it easy to approximate expected mean values, but very difficult to reproduce the expected variation in values, especially across a range of datasets and especially for binomial data.

Carlisle also uses the notion of 'central limit theorem' in his analysis of continuous data. Variously expressed, this has several important consequences for large datasets. First, the theorem states that when we take multiple samples from a population and measure a characteristic of interest, then a histogram of the sample means resembles ever closer a normal distribution with an increasing number of samples, *even if the histogram of the actual population is not normally distributed*. This is a surprising but very fundamental and robustly proven principle of statistics (Fig. 4). Another aspect of the theorem is that as the number of samples increases, not only does the mean of all the samples ever more closely approximate the population mean, but its variance (known technically as the standard error of the mean) becomes smaller in a precise way. All this is important because while any single random sample may differ greatly from another random sample, combining their means should follow the predictions of central limit theorem. What Carlisle found for Fujii's data is that even when the 'less unusual' data from trials were sequentially combined, the results became *more*, rather than *less*, deviant from expected distributions (see the dotted black line in Fig. 14 of Carlisle's paper [2]).

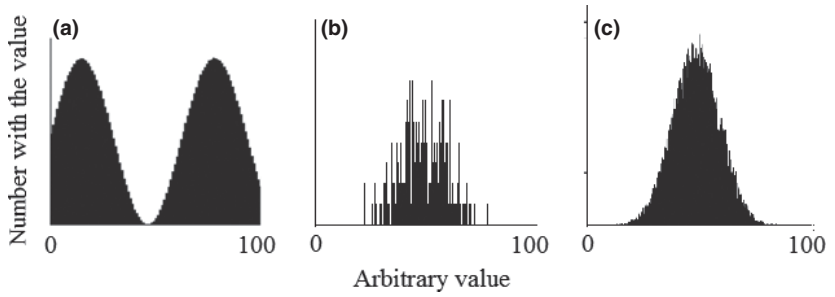

Figure 4 Demonstration of central limit theorem. The underlying distribution of this characteristic (arbitrary units, x-axis) resembles a sine wave (a), where there are a very large number of data points (> 200 000). Repeated random sampling of 100 values 100 times from this population of points (b) and 100 values 10 000 times (c), and plotting the means of these sample values, yields a pattern ever closer to a normal distribution. Readers can check other distributions at: http://elonen.iki.fi/articles/centrallimit/index.en.html#demo.

Does biological variation matter?

> *"In genetical work also, duplicates rarely agree unless they are faked."* [1].

One potential defence of an unusually-distributed dataset is that the vagaries of biology cause it to be so: patients can be odd or respond strangely. Yet even biology shows certain mathematically predictable patterns and statistical analysis can counter this 'biological defence' of unusual data in at least two ways.

The first rests upon an observation developed by GH Hardy. Many traits are strongly determined by genetic factors, and some are determined by 'dominant' alleles. It might be predicted that this would cause the population characteristic to gravitate towards the dominant trait over succeeding generations, resulting in ever narrower variations in human phenotype. But in contrast it is clear that the overall variation in many characteristics (e.g. height, weight) within a population remains constant (and often Gaussian) from one generation to the next. How can the constancy of Gaussian distribution be reconciled with a dominant effect of

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certain alleles? The answer is in part explained by the Hardy-Weinberg Law, which I have discussed before [6]. According to the Law, allele distributions are fixed for all generations (given conditions such as random mating and no breeder selection). For a characteristic governed only by two alleles, the relative proportions of homozygote recessives (*pp*), heterozygotes (*pq*) and homozygote dominants (*qq*) follow the distribution p^2:2*pq*:q^2. These are (as Hardy well knew) the same proportions that describe the outcome of tossing two coins, represented by a binomial distribution (Equation 3, above, whose coefficients also correspond to the 2nd line of Pascal's triangle – 1:2:1). Thus for binary characteristics, distributions should follow the proportions predicted by the Hardy-Weinberg Law, and any other proportions reported by an author must be regarded as unusual. Furthermore, Fisher extended this argument to multi-allele traits [7, 8] to show that where a large number of alleles made a small contribution to a continuous trait (e.g. height), the trait (i.e. phenotype in the population) would be normally distributed but each of the allele pairs would nonetheless follow the Hardy-Weinberg equilibrium (Fig. 5). Therefore, it we wished to fabricate a dataset, we would face the difficult task of ensuring that the phenotype distribution in the population was Gaussian, but that the corresponding allele distributions in our invented data (if later discoverable from the information provided) conformed to the predictions of the Hardy-Weinberg Law (adapted for multiple alleles). This is easy for nature, but not so easy for us. Carlisle did not analyse Fujii's data in this way, but the recent discovery of at least one allele associated with postoperative nausea and vomiting (and whose distribution in the population follows Hardy-Weinberg equilibrium) makes possible further analysis of Fujii's voluminous data using these genetic principles [9].

(a)

	h^+	$2h^0$	h^-
h^+	h^+h^+ 72 cm	$2(h^+h^0)$ 70 cm	h^+h^- 68 cm
$2h^0$	$2(h^0h^+)$ 70 cm	$4(h^+h^0)$ 68 cm	$2(h^0h^-)$ 66 cm
h^-	h^-h^+ 68 cm	$2(h^0h^+)$ 66 cm	h^-h^- 64 cm

(b)

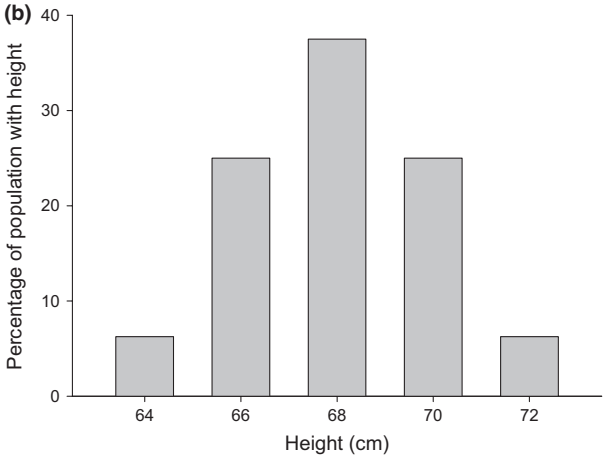

Figure 5 Fisher's argument to demonstrate how a normal distribution in phenotype can arise even when alleles follow the proportions predicted by Hardy-Weinberg equilibrium (for multiple alleles). Suppose three alleles determine height (average 68 cm): h^0 (neutral), h^+ (which adds 2 cm) and h^- (which subtracts 2 cm); h^0 is twice as frequent than the others, which are equally frequent. (a): Punnett square for the population (explained in ref [6], where the characters in bold represent the gametes that combine) with the relative resulting proportions. (b): the histogram of the resulting heights in the population resembling a normal distribution. Adding more loci to the model results in an even smoother histogram.

A second reason why it is difficult to invent biology is that many biological traits are themselves inter-related. If we invent one trait then we commit ourselves automatically to inventing several others. Simple examples might be the relationships between height, weight and body mass index, or those between tidal volume, frequency and inspiratory/expiratory time. Other biological traits are exclusive. To adopt the example used by Haldane [1]: suppose three classes of animal have frequencies *p*1, *p*2, *p*3, and the total is 200. If we invent the ratios 50 *p*1 and 40 *p*2 to satisfy the conclusion we wish to reach, in *p*3 (perhaps of no imme-

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diate interest) *has* to be 110. Yet, a different value may be needed to satisfy other biological ratios and interactions.

Conclusions

> *"For a successful technology, reality must take precedence over public relations, for nature cannot be fooled."* [11].

Those wishing to invent data have a hard task. They must ensure that all the data satisfy several layers of statistical cross-examination. Haldane referred to these as the 'orders of faking' [1]. In his words, 'first-order faking' is to ensure simply that the mean values match what is expected. For his 'second-order faking', things become more difficult since the variances of these means must also be within those expected, and further consistent with several possibly inter-related variables. His 'third-order faking' is extremely difficult because the results must also match several established laws of nature or mathematics, described by patterns like central limit theorem, the Hardy-Weinberg Law, the law of conservation of energy or mass, and so on. It is therefore always so much easier actually to do the experiment than to invent its results.

It is the very motivation to publish so much that is the undoing of those whose work is questioned or retracted. High publication rates are evident in the retracted work of Reuben and Boldt [12], and the sheer volume of data produced by Fujii is astonishing [2]. Toss a coin just twice and if it gives two heads then nobody notices the loading (the chance of this in a fair coin is anyway 25%). But a 100 heads in 100 tosses is probably more than chance (Fig. 1). These high publication rates leave a rich source of data for us to analyse, so that we can learn aberrant patterns and in time, detect much earlier the warning signs. Carlisle is to be congratulated: his is an astonishing, altruistic piece of work that helps expunge the literature of some (at best) highly unusual data.

The purpose of experimentation is to learn about nature. If the results of experiments are not genuine, then however prolific, influential or politically powerful their author, the results will not withstand statistical scrutiny, cannot be repeated, or will lead to models for our understanding of nature that are so bizarre as to be proven false. For nature cannot be fooled.

Competing interests

No external funding or competing interests declared.

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Steven L. Shafer, MD
Editor-in-Chief

March 7, 2012

To our readers:

Toho University today announced the retraction of eight manuscripts by Dr. Yoshitaka Fujii published under its auspices, as well as the dismissal of Dr. Fujii from Toho University. The manuscripts have been retracted for lack of proper ethics approval. Specific manuscripts that have been retracted are:

1. Fujii Y, Itakura M. Antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. Otolaryngol Head Neck Surg. 2011;144:206-9

2. Fujii Y, Itakura M. A prospective, randomized, double-blind, placebo-controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery. Clin Ther. 2010;32:1633-7

3. Fujii Y, Itakura M. Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2010;24:692-6

4. Fujii Y, Itakura M. A comparison of pretreatment with fentanyl and lidocaine preceded by venous occlusion for reducing pain on injection of propofol: a prospective, randomized, double-blind, placebo-controlled study in adult Japanese surgical patients. Clin Ther. 2009;31:2107-12

5. Fujii Y, Itakura M. Low-dose propofol to prevent nausea and vomiting after laparoscopic surgery. Int J Gynaecol Obstet. 2009;106:50-2

6. Fujii Y, Itakura M. Pretreatment with flurbiprofen axetil, flurbiprofen axetil preceded by venous occlusion, and a mixture of flurbiprofen axetil and propofol in reducing pain on injection of propofol in adult Japanese surgical patients: a prospective, randomized, double-blind, placebo-controlled study. Clin Ther. 2009;31:721-7

7. Fujii Y, Itakura M. Comparison of propofol, droperidol, and metoclopramide for prophylaxis of postoperative nausea and vomiting after breast cancer surgery: a prospective, randomized, double-blind, placebo-controlled study in Japanese patients. Clin Ther. 2008;30:2024-9

8. Fujii Y, Itakura M. Comparison of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, parallel-group, placebo-controlled study. Clin Ther. 2008;30:280-6.

The announcement also identified a single manuscript for which there was evidence of appropriate IRB approval:

Fujii Y, Itakura M. Efficacy of the lidocaine/flurbiprofen axetil combination for reducing pain during the injection of propofol. Minerva Anestesiol. 2011;77:693-7

The announcement by Toho University did not address 13 additional manuscripts by Dr. Fujii that list Toho University as the academic institution of record:

1. Fujii Y. Management of postoperative nausea and vomiting in women scheduled for breast cancer surgery. J Anesth. 2011;25:917-22

2. Fujii Y. Current review of ramosetron in the prevention of postoperative nausea and vomiting. Curr Drug Saf. 2011;6:122-7

3. Fujii Y. Management of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2011;25:691-5

4. Fujii Y. Prevention of nausea and vomiting during termination of pregnancy. Int J Gynaecol Obstet. 2010;111:3-7

5. Fujii Y. Clinical management of postoperative vomiting after strabismus surgery in children. Curr Drug Saf. 2010;5:132-48

6. Fujii Y. [Postoperative nausea and vomiting and their sex differences]. Masui. 2009;58:59-66

7. Fujii Y. Current management of vomiting after tonsillectomy in children. Curr Drug Saf. 2009;4:62-7

8. Fujii Y. Clinical strategies for preventing postoperative nausea and vomitting after middle ear surgery in adult patients. Curr Drug Saf. 2008;3:230-9

9. Fujii Y. The benefits and risks of different therapies in preventing postoperative nausea and vomiting in patients undergoing thyroid surgery. Curr Drug Saf. 2008;3:27-34

10. Fujii Y. Prevention of emetic episodes during cesarean delivery performed under regional anesthesia in parturients. Curr Drug Saf. 2007;2:25-32

11. Fujii Y, Nakayama M. Prevention of pain due to injection of propofol with IV administration of lidocaine 40 mg + metoclopramide 2.5, 5, or 10 mg or saline: a

randomized, double-blind study in Japanese adult surgical patients. Clin Ther. 2007;29:856-61

12. Fujii Y. Prophylaxis of postoperative nausea and vomiting in patients scheduled for breast surgery. Clin Drug Investig. 2006;26:427-37

13. Fujii Y, Nakayama M. Influence of age on flurbiprofen axetil requirements for preventing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, vehicle-controlled, parallel-group, dose-ranging study. Clin Ther. 2006;28:1116-22

These manuscripts were retracted because of lack of IRB approval. The announcement by Toho University did not address the possibility of fraud. However, the April 2000 issue of *Anesthesia & Analgesia* includes a disturbing Letter to the Editor by Kranke, Apfel, and Roewer alleging research fraud by Dr. Fujii[1] The title of the letter says everything you need to know: "Reported data on granisetron and postoperative nausea and vomiting by Fujii et al. are incredibly nice!" In 2001 Kranke and colleagues published a manuscript demonstrating consistent discrepancies between data published by Fujii supporting the efficacy of granisetron and data published by other investigators.[2]

The announcement by Toho University follows a joint effort over the past two years by multiple Editors-in-Chief to follow up on the Letter to the Editor in *Anesthesia & Analgesia* and lingering concerns about the integrity of Dr. Fujii's published research. There will be further disclosure over the next few days by the involved editors. I want to explicitly thank Dr. Steve Yentis, Editor-in-Chief of *Anaesthesia*, who raised the question two years ago about the integrity of Dr. Fujii's published studies and our responsibility to pursue allegations of misconduct more than 10 years old. I also want to thank Dr. Donald Miller, Editor-in-Chief of the *Canadian Journal of Anesthesia*, who is responsible for the inquiry conducted by Toho University that led to the public acknowledgment that Dr. Fujii's work was compromised and his dismissal from Toho University.

These findings raise considerable concern about the integrity of the papers published by Dr. Fujii in *Anesthesia & Analgesia*. The following manuscripts in *Anesthesia & Analgesia* may represent fraudulent research:

1. Fujii Y, Uemura A. The effects of different dobutamine infusion rates on hypercapnic depression of diaphragmatic contractility in pentobarbital-anesthetized dogs. Anesth Analg. 2007;105:1379-84 (University of Tsukuba)

2. Fujii Y, Uemura A, Toyooka H. The recovery profile of reduced diaphragmatic contractility induced by propofol in dogs. Anesth Analg. 2004;99:113-6 (University of Tsukuba)

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24. Fujii Y, Tanaka H, Tsuruoka S, Toyooka H, Amaha K. Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy. Anesth Analg. 1994;78:80-3 (Toride Kyodo General Hospital)

These manuscripts are from two institutions: the University of Tsukuba (21 papers) and Toride Kyodo General Hospital (3 papers). I will contact each institution requesting an inquiry into the integrity of these manuscripts. Although these manuscripts date back to 1994, we must make a determination what papers are valid, and what papers represent research fraud.

Following publication of the Letter to the Editor from Kranke and colleagues in April 2000, along with a non-specific response from Dr. Fujii, there was no follow-up on the allegation of data manipulation. There was no request for an institutional review of Dr. Fujii's research. Additionally, *Anesthesia & Analgesia* published 11 additional manuscripts by Dr. Fujii following the 2000 allegations of research fraud.

The Journal's response to the allegations of research fraud in the 2000 Letter to the Editor by Kranke and colleagues was inadequate. The subsequent submissions to the Journal by Dr. Fujii should not have been published without first vetting the allegations of fraud. I apologize to our readers, and the patients we serve, for the manner in which the allegations of fraud were handled by *Anesthesia & Analgesia.*

Sincerely,

Steven L. Shafer, MD
Editor-in-Chief
Anesthesia & Analgesia

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Canadian Journal of Anesthesia
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Expression of Concern

Online posting to the *Canadian Journal of Anesthesia*

Release Date: March 13, 2012

To our readers:

In 2011, the *Canadian Journal of Anesthesia* received an article submission entitled: "Effects of colforsin daropate on hypercapnic depression of diaphragmatic contractility in pentobarbital-anesthetized dogs". The authors were Yoshitaka Fujii, MD and Aki Uemura, MD from the First Department of Anesthesiology, Toho University School of Medicine. At the time of article submission, we were aware of ongoing concerns regarding Dr. Fujii's work that extended as far back as 2000. A Letter to the Editor by Drs. Kranke *et al*.[1] published in *Anesthesia & Analgesia* raised concerns about the implausibility of data from a large number of articles published by Dr. Fujii across a number of journals, including the *Canadian Journal of Anesthesia.* We were also aware of an ongoing analysis of 169 randomized controlled trials being undertaken by Dr. John Carlisle, the results of which were recently published in *Anaesthesia*.[2] This unique article provides overwhelming statistical evidence that "the distribution of continuous and categorical variables reported in Fujii's papers, both animal and human, are extremely unlikely to have arisen by chance and if so, in many cases with likelihoods that are infinitesimally small."

As a result of an internal investigation in the Department of Anesthesia at Toho University, it was determined that the article submitted to the *Canadian Journal of Anesthesia* in 2011 had no ethical approval but also that the data had been fabricated. These events resulted in the launch of a more extensive review by the Investigating Committee of the Faculty of Medicine at Toho University. The results of the university Discipline Committee were released on March 8, 2012:

“Since all of Dr. Fujii’s clinical studies that appeared in these 9 publications [below] were conducted at Ushiku Aiwa General Hospital, which has no relation to his research activity in Toho University, the investigation committee contacted the head of the hospital. As far as the head of the hospital knows, there was only one clinical study listed by Dr. Fujii as having been conducted at the hospital. The other eight clinical studies were conducted without any ethics committee’s approval, and this was judged sufficient to decide that 8 of his publications (No. 2 to 9) should be retracted since they did not conform to the global standard of ethics for clinical studies. After the investigation, the committee asked Dr. Yoshitaka Fujii and his co-author, Dr. Michiyo Itakura, to explain the whole circumstances. Dr. Fujii admitted that the clinical studies were done without any ethics committee’s approval. Dr. Itakura, however, was not involved in this misconduct. Dr. Yoshitaka Fujii sent letters of retraction to the affected journals. We organized a disciplinary committee and decided that a disciplinary dismissal was appropriate for Dr. Fujii effective from February 29, 2012. Dr. Fujii has already been dismissed from Toho University.”

Below is the list of nine publications in which it was determined that Dr. Fujii did not receive ethical approval:

1. *Fujii Y, Itakura M.* Efficacy of the lidocaine/flurbiprofen axetil combination for reducing pain during the injection of propofol. Minerva Anestesiol 2011 Jul; 77(7): 693-7.

2. *Fujii Y, Itakura M.* Antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. Otolaryngol Head Neck Surg 2011 Feb; 144(2): 206-9.

3. *Fujii Y, Itakura M.* A prospective, randomized, double-blind, placebo-controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery. Clin Ther 2010 Aug; 32(9): 1633-7.

4. *Fujii Y, Itakura M.* Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc 2010 Mar; 24(3): 692-6.

5. *Fujii Y, Itakura M.* A comparison of pretreatment with fentanyl and lidocaine preceded by venous occlusion for reducing pain on injection of propofol: a prospective, randomized, double-blind, placebo-controlled study in adult Japanese surgical patients. Clin Ther 2009 Oct; 31(10): 2107-12.

6. Fujii Y, Itakura M. Low-dose propofol to prevent nausea and vomiting after laparoscopic surgery. Int J Gynaecol Obstet 2009 Jul; 106(1): 50-2.

7. *Fujii Y, Itakura M.* Pretreatment with flurbiprofen axetil, flurbiprofen axetil preceded by venous occlusion, and a mixture of flurbiprofen axetil and propofol in reducing pain on injection of propofol in adult Japanese surgical patients: a prospective, randomized, double-blind, placebo-controlled study. Clin Ther 2009 Apr; 31(4): 721-7

8. *Fujii Y, Itakura M.* Comparison of propofol, droperidol, and metoclopramide for prophylaxis of postoperative nausea and vomiting after breast cancer surgery: a prospective, randomized, double-blind, placebo-controlled study in Japanese patients. Clin Ther 2008 Nov; 30(11): 2024-9.

9. *Fujii Y, Itakura M.* Comparison of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, parallel-group, placebo-controlled study. Clin Ther 2008 Feb; 30(2): 280-6.

The announcement by Toho University follows a joint effort by editors-in-chief of a number of anesthesia journals. I extend my personal thanks to Dr. Steven Shafer, Editor-in-Chief of *Anesthesia & Analgesia*, and Dr. Steven Yentis, Editor-in-Chief of *Anaesthesia*, both of whom have played pivotal roles in pursuing the question of possible scientific misconduct of Dr. Fujii's work. While none of the nine articles on the above list was published in the *Canadian Journal of Anesthesia*, the egregious ethical misconduct that has already been confirmed and the overwhelming concerns of scientific misconduct now cast a shadow of serious doubt relating to every one of the articles that Dr. Yoshitaka Fujii has ever published. Accordingly, it is important that we provide a complete list of articles written by Dr. Yoshitaka Fujii that were published in the *Canadian Journal of Anesthesia*:

- *Ebata T, Fujii Y, Toyooka H*. Dobutamine increases diaphragmatic contractility in dogs. Can J Anaesth 1992; 39: 375-80.

- *Fujii Y, Toyooka H, Ebata T, Amaha K.* Contractility of fatigued diaphragm is improved by dobutamine. Can J Anaesth 1993; 40: 453-8.
- *Fujii Y, Tanaka H, Toyooka H*. Reduction of postoperative nausea and vomiting with granisetron. Can J Anaesth 1994; 41: 291-4.
- *Fujii Y, Toyooka H, Amaha K*. Nicardipine enhances diaphragmatic fatigue. Can J Anaesth 1994; 41: 435-9.
- *Fujii Y, Tanaka H, Toyooka H.* Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting. Can J Anaesth 1994; 41: 794-7.
- *Fujii Y, Tanaka H, Toyooka H*. Circulatory responses to laryngeal mask airway insertion or tracheal intubation in normotensive and hypertensive patients. Can J Anaesth 1995; 42: 32-6.
- *Fujii Y, Toyooka H, Amaha K*. Amrinone improves contractility of fatigued diaphragm in dogs. Can J Anaesth 1995; 42: 80-6.
- *Fujii Y, Tanaka H, Toyooka H.* Granisetron-dexamethasone combination reduces postoperative nausea and vomiting. Can J Anaesth 1995; 42: 387-90.
- *Fujii Y, Tanaka H, Saitoh Y, Toyooka H*. Effects of calcium channel blockers on circulatory response to tracheal intubation in hypertensive patients: nicardipine versus diltiazem. Can J Anaesth 1995; 42: 785-8.
- *Fujii Y, Tanaka H, Toyooka H*. Prevention of postoperative nausea and vomiting with granisetron: a randomized, double-blind comparison with droperidol. Can J Anaesth 1995; 42: 852-6.
- *Saitoh Y, Fujii Y, Toyooka H, Amaha K.* Post-tetanic burst count: a stimulating pattern for profound neuromuscular blockade. Can J Anaesth 1995; 42: 1096-100.
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- *Fujii Y, Toyooka H, Tanaka H*. Antiemetic effects of granisetron on postoperative nausea and vomiting in patients with and without motion sickness. Can J Anaesth 1996; 43: 110-4.
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- *Fujii Y, Tanaka H, Toyooka H*. Prophylactic antiemetic efficacy of granisetron in patients with and without previous postoperative emesis. Can J Anaesth 1997; 44: 273-7.

- *Fujii Y, Tanaka H, Toyooka H*. Granisetron reduces the incidence and severity of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth 1997; 44: 396-400.
- *Fujii Y, Tanaka H, Toyooka H*. Granisetron reduces postoperative nausea and vomiting throughout menstrual cycle. Can J Anaesth 1997; 44: 489-93.
- *Fujii Y, Toyooka H, Tanaka H*. Prevention of PONV with granisetron, droperidol and metoclopramide in female patients with history of motion sickness. Can J Anaesth 1997; 44: 820-4.
- *Fujii Y, Toyooka H, Tanaka H*. Cardiovascular responses to tracheal extubation or LMA removal in normotensive and hypertensive patients. Can J Anaesth 1997; 44: 1082-6.
- *Fujii Y, Saitoh Y, Tanaka H, Toyooka H*. Prevention of PONV with granisetron, droperidol or metoclopramide in patients with postoperative emesis. Can J Anaesth 1998; 45: 153-6.
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- *Fujii Y, Saitoh Y, Tanaka H, Toyooka H*. Prophylactic antiemetic therapy with granisetron-droperidol combination in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 1998; 45: 541-4.
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- *Fujii Y, Saitoh Y, Takahashi S, Toyooka H*. Diltiazem-lidocaine combination for the attenuation of cardiovascular responses to tracheal intubation in hypertensive patients. Can J Anaesth 1998; 45: 933-7.
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- *Fujii Y, Saitoh Y, Takahashi S, Toyooka H*. Combined diltiazem and lidocaine reduces cardiovascular responses to tracheal extubation and anesthesia emergence in hypertensive patients. Can J Anesth 1999; 46: 952-6.
- *Fujii Y, Saitoh Y, Tanaka H, Toyooka H*. Ramosetron vs granisetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Can J Anesth 1999; 46: 991-3.
- *Takahashi S, Fujii Y, Hoshi T, Inomata S, Miyabe M, Toyooka H*. Modifications of the hemodynamic consequences of theophylline intoxication with landiolol in halothane-anesthetized dogs. Can J Anesth 2000; 47: 265-72.
- *Hoshi T, Fujii Y, Takahashi S, Toyooka H*. Effect of xenon on diaphragmatic contractility in dogs. Can J Anesth 2000; 47: 819-22.
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- *Saitoh Y, Kaneda K, Fujii Y, Oshima T*. Nicorandil accelerates recovery of neuromuscular block caused by vecuronium. Can J Anesth 2001; 48: 28-33.
- *Fujii Y, Toyooka H*. High-dose colforsin daropate increases diaphragmatic contractility in dogs. Can J Anesth 2002; 49: 877-9.
- *Takahashi S, Fujii Y, Hoshi T, Uemura A, Miyabe M, Toyooka H*. Milrinone attenuates the negative inotropic effects of landiolol in halothane-anesthetized dogs. Can J Anesth 2003; 50: 830-4.
- *Nakano M, Fujii Y*. Prevention of nausea and vomiting after dental surgery: a comparison of small doses of propofol, droperidol, and metoclopramide. Can J Anesth 2003; 50: 1085.
- *Fujii Y*. Pretreatment with flurbiprofen axetil and venous occlusion to reduce pain during injection of propofol. Can J Anesth 2004; 51: 1047-8.
- *Numazaki M, Fujii Y*. Antiemetic efficacy of propofol at small doses for reducing nausea and vomiting following thyroidectomy. Can J Anesth 2005; 52: 333-4.
- *Fujii Y, Nakayama M*. A lidocaine/metoclopramide combination decreases pain on injection of propofol. Can J Anesth 2005; 52: 474-7.

The editors of the affected journals will jointly contact the Deans of the Faculties of Medicine of the six universities from which Dr. Fujii published his work to alert them of these concerns and to request that they provide unequivocal evidence of Institutional Review Board approval and data veracity regarding all of the studies cited in the Carlisle article. This review will be complex as it involves a number of institutions. In the absence of the aforementioned documentation, it is possible that many or all of the affected articles may be retracted in due course.

In general, health practice and policy is rarely changed based on the results of a single primary study. More often, change happens after a systematic review or practice guideline (resulting from a systematic review). In the case of Dr. Fujii, it will also be important to ascertain whether any of his primary research has been included in systematic reviews, as the results could be potentially misleading until such time as they can be re-analyzed without the problem primary studies.

We deeply regret the shadow of serious doubt that has been cast over such a large body of scientific literature. I have previously expressed my personal views regarding scientific misconduct.[3] In a recent editorial,[4] Dr. Elizabeth Wager, Chair of the Committee on Publication Ethics, explored the challenging and complex issue concerning who is responsible for investigating suspected research misconduct. As stated by Dr. Wager in her recent editorial, “Research misconduct is hard to prevent because it represents a systems

failure, so its causes and solutions are multifactorial. Similarly, systems for investigating misconduct appear to be difficult to establish, fund and monitor…unless we establish better methods for investigating misconduct, researchers and clinicians will be left with lingering doubt about the purity and therefore trustworthiness of the evidence they rely on to make decisions."

Donald R. Miller, MD
Editor-in-Chief
Canadian Journal of Anesthesia

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3. *Miller DR*. Special notice to readers and authors on scientific misconduct. Can J Anesth 2009; 56: 408-11.
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Canadian Journal of Anesthesia/Journal canadien d'anesthésie
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April 6, 2012

Professor Kuroda, Dean, Toho University
Professor Takamatsu, Dean, Toho University
Professor Igarashi, Director, Tsukuba University Hospital
Professor Tanaka, Chairman, Department of Anesthesiology, University of Tsukuba
Professor Shintani, Director, JA Toride Medical Center
Professor Makita, Chairman, Department of Anesthesiology, JA Toride Medical Center
Professor Miyasaka, Director, Tokyo Medical and Dental University
Prof Makita, Chairman, Department of Anesthesiology, Tokyo Medical and Dental University
Professor Murakawa, Chairman, Department of Anesthesia, Fukushima Medical University
Professor Kagawa, Chairman, Department of Anesthesiology, Hyogo Prefectural Kobe Children's Hospital
Professor Maekawa, Chairman, Department of Anesthesiology and Perioperative Medicine, Kobe University

Re: Investigation into Research by Yoshitaka Fujii

Dear Professors Kuroda, Takamatsu, Igarashi, Tanaka, Shintani, Makita, Miyasaka, Makita, Murakawa, Kagawa, and Maekawa:

The undersigned Editors-in-Chief are grateful to the University of Toho for investigating the studies of Dr Yoshitaka Fujii, and note the announcement of his dismissal (http://www.toho-u.ac.jp/english/Information/march_6_2012.html).

The journal *Anaesthesia* has published a manuscript that appears to present overwhelming evidence that the distributions of many variables reported by Dr Fujii, in 168 published trials conducted under the auspices of your respective institutions, could not have occurred by chance (Carlisle JB, The analysis of 169 randomised controlled trials to test data integrity. Anaesthesia 2012, Epub 8 Mar 2012; http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2044.2012.07128.x/full). A copy of this manuscript follows this letter. While the title of the paper states 169 papers, there is 1 duplicated reference, so the actual number of papers analyzed in the manuscript is 168.

Appendix 1 lists 193 papers published by Dr. Fujii, based on a reconciliation of Appendix 1 in the Carlisle analysis, a comprehensive Medline search, and correspondence among the undersigned Editors-in-Chief. There are 168 papers from the Carlisle analysis, and 25 not included in the Carlisle analysis. Papers <u>not</u> included in the Carlisle analysis are indicated with an asterisk in Appendix 1.

Appendix 2 lists the papers published by Dr. Fujii sorted by the institution under whose auspices the research was conducted. We are turning to you for a determination of the authenticity of those papers listed in Appendix 2 as representing research <u>attributed by Dr. Fujii to your institution</u>.

The undersigned Editors-in-Chief intend to retract manuscripts from their respective journals based on the evidence of fraud demonstrated in the analysis by Carlisle. However, prior to retraction we wish to offer your institution the opportunity to attest to the integrity of any manuscript conducted under the auspices of your institution, as listed in Appendix 2.

For each study listed in Appendix 2 we ask your institution to state the following:

1. that the study occurred as represented in the paper;
2. that you have examined the original research data and have verified that the data are authentic; and
3. that appropriate research ethical approval for the study was obtained.

Our request follows the guidelines published by the Committee on Publication Ethics. Quoting from Wager E, Kleinert S, on behalf of COPE Council. Cooperation between research institutions and journals on research integrity cases: guidance from the Committee on Publication Ethics (COPE):[1]

"*Research and publication misconduct may not be an isolated incident. In many cases, when serious misconduct comes to light, investigation of the researcher's earlier work reveals further problems. Therefore, when a researcher is found to have committed serious misconduct (such as data fabrication, falsification or plagiarism) the institution should review all the individual's publications, including those published before the proven misconduct took place. In such cases, it may be necessary to alert previous employers to enable them to review work carried out by the discredited researcher when working at their institution, to determine the reliability of publications arising from that work.*"

Fraudulent research must be retracted in a timely manner. If we do not hear from you by June 30 2012 we will assume that you do not intend to respond. If you do intend to respond, please provide a timeline for your assessment.

This is not a confidential communication. To provide transparency to our readers, we intend to post this request letter, and your response, on our journal websites.

Please direct your response to Dr. Steven Shafer at steven.shafer@stanford.edu.

We appreciate your assistance with this request.

On behalf of our respective journals,

Lars S. Rasmussen
Editor-in-Chief, ***Acta Anaesthesiologica Scandinavica***

[1] http://publicationethics.org/files/Research_institutions_guidelines_final.pdf

Steven M. Yentis
Editor-in-Chief, ***Anaesthesia***

Neville Gibbs
Editor-in-Chief, ***Anaesthesia & Intensive Care***

Masashi Kawamoto
Editor-in-Chief, ***Anesthesia and Resuscitation***

Steven L. Shafer
Editor-in-Chief, ***Anesthesia & Analgesia***

Charles S. Reilly
Editor-in-Chief, ***British Journal of Anaesthesia***

Donald R. Miller
Editor-in-Chief, ***Canadian Journal of Anesthesia/Journal canadien d'anesthésie***

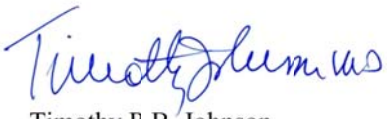
Robert Gaiser
Editor-in-Chief, ***Clinical Anesthesia***

Jasbir Singh
Editor, ***Clinical Drug Investigation***

Phil Walson
Editor-in-Chief, ***Clinical Therapeutics***

Martin R. Tramèr
Editor-in-Chief, ***European Journal of Anaesthesiology***

Robin Russell
Editor-in-Chief, ***International Journal of Obstetric Anesthesia***



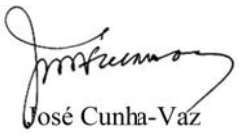
Timothy R.B. Johnson
Editor-in-Chief, ***International Journal of Gynecology and Obstetrics***

Kazuyoshi Hirota
Editor-in-Chief, ***Journal of Anesthesia***

James Hupp
Editor-in-Chief, ***Journal of Oral and Maxillofacial Surgery***

Davide Chiumello
Editor-in-Chief, ***Minerva Anestesiologica***

James Scott
Editor-in-Chief, ***Obstetrics and Gynecology***



José Cunha-Vaz
Editor-in-Chief, ***Ophthalmologica***

Neil Morton
Editor-in-Chief, ***Pediatric Anesthesia***

Alfred Cuschieri, Mark Talamini

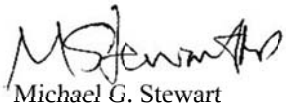
Sir Alfred Cuschieri, Mark Talamini
Editors-in-chief, ***Surgical Endoscopy***

Shahla Masood

Shahla Masood
Editor-in-Chief, ***The Breast Journal***

Derek Alderson

Derek Alderson
Editor-in-Chief, ***The British Journal of Surgery***



Michael G. Stewart
Editor-in-Chief, ***The Laryngoscope***

Acta Anaesthesiologica Scandinavica

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4. Fujii Y, Tanaka H, Toyooka H. Prevention of nausea and vomiting in female patients undergoing breast surgery:a comparison with granisetron, droperidol, metoclopramide and placebo. Acta Anaesthesiol Scand 1998;42:220-4
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9. Hoshi T, Fujii Y, Toyooka H. Comparative effects of xenon and nitrous oxide on diaphragmatic contractility in dogs. Acta Anaesthesiol Scand 2002;46:699-702*

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American Journal of Therapeutics

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【資料 3 - 1】

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
C	1		○	○					麻酔	横隔膜疲労における神経筋伝達不全の関与	大島勉	東京都立広尾病院	藤井善隆	東京医科歯科大学医学部麻酔蘇生学教室	豊岡秀訓	東京医科歯科大学医学部　麻酔蘇生学教室	宇田川友之	東京医科歯科大学医学部　麻酔蘇生学教室	横山訓典	東京医科歯科大学医学部麻酔蘇生学教室	天羽敬祐	東京医科歯科大学医学部麻酔蘇生学教室	1990	犬						
C	2	○		○				○	Journal of Anesthesia	Diaphragmatic fatigue and its recovery are influenced by cardiac output	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院							1991	犬					20	
C	3		○	○					麻酔	重篤な低心拍出量の横隔膜疲労および回復に及ぼす影響と神経筋伝達不全の関与	藤井善隆	取手協同病院	大島勉	東京医科歯科大学医学部麻酔蘇生学教室	豊岡秀訓	東京医科歯科大学医学部　麻酔蘇生学教室	宇田川友之	東京医科歯科大学医学部　麻酔蘇生学教室	江畑俊哉	東京医科歯科大学医学部麻酔蘇生学教室	天羽敬祐	東京医科歯科大学医学部麻酔蘇生学教室	1991	犬				犬	20	
C	4		○	○					Anesthesia and Resuscitation = 麻酔と蘇生	Prostaglandin E1の横隔膜収縮力に及ぼす影響	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1991	犬	プロスタグランディン				10	
C	5	○		○				○	Canadian Journal of Anesthesia	Dobutamine increases diaphragmatic contractility in dogs	江畑俊哉	東京医科歯科大学医学部附属病院	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1992	犬					24	
C	6		○	○					Anesthesia and Resuscitation = 麻酔と蘇生	横隔膜収縮力に及ぼすNicardipineの影響	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1992	犬	ニカルジピン				11	
C	7		○	○					Anesthesia and Resuscitation = 麻酔と蘇生	プロスタグランジンE1の呼吸因子−1回換気量,分時換気量−に及ぼす影響	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1992	呼吸	プロスタグランディン			外科 耳科		30
C	8	○		○				○	Canadian Journal of Anesthesia	Contractility of fatigued diaphragm is improved by dobutamine	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院	江畑俊哉	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院					1993	犬					20	
B	9		○	○					麻酔	ドロペリドールの術後制吐効果に対する検討	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1993	PONV	ドロペリドール	メトクロプラシド		婦人科		60
B	10		○	○					麻酔	小児におけるラリンジアルマスクの循環動態と術後咽頭痛,嗄声に及ぼす影響	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部　麻酔蘇生学教室							1993	咽頭痛				小児		40
B	11	○		○			RCTDB	○	Canadian Journal of Anesthesia	Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1994	PONV	グラニセトロン			婦人科 大手術		100
B	12	○		○			RCT	○	Canadian Journal of Anesthesia	Reduction of postoperative nausea and vomiting with granisetron	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1994	PONV				婦人科 大手術		60
C	13	○		○				○	Canadian Journal of Anesthesia	Nicardipine enhances diaphragmatic fatigue	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院							1994	犬					20	
B	14	○		○				○	Journal of Anesthesia	Airway occlusion pressure is an indicator of respiratory depression with isoflurane	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院					1994	気道	イソフルラン			婦人科 大手術		10
C	15	○		○				○	Journal of Anesthesia	Effects of dobutamine on the fatigued diaphragm: A comparison with dopamine	藤井善隆	取手協同病院	宇田川友之	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1994	犬	ドブタミン	ドーパミン			26	
B	16	○		○				○	Anesthesia and Analgesia	Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy.	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Tsuruoka Shin	取手協同病院(脳神経外科)	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院			1994	中大脳動脈				胆摘		10
C	17		○	○					Anesthesia and Resuscitation = 麻酔と蘇生	実験的横隔膜疲労におけるニカルジピンの横隔膜収縮力に及ぼす影響	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1994	犬	ニカルジピン				15	
C	18		○	○					日本臨床麻酔学会誌	膝関節鏡手術の麻酔方法に対する検討	藤井善隆		田中弘彦										1994	不要						
B	19	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prevention of postoperative nausea and vomiting with granisetron: a randomised, double-blind comparison with droperidol	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1995	PONV	グラニセトロン			婦人科 大手術		100
B	20	○		○			RCTDB	○	Canadian Journal of Anesthesia	Granisetron-dexamethasone combination reduces postoperative nausea and vomiting	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1995	PONV	グラニセトロン	デキサメサゾン		婦人科 大手術		88
B	21	○		○			RCTDB	○	Canadian Journal of Anesthesia	Circulatory responses to laryngeal mask airway insertion or tracheal intubation in normotensive and hypertensive patients	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1995	挿管反応				全科		46
B	22	○		○				○	Canadian Journal of Anesthesia	Effects of calcium blockers on circulatory response to tracheal intubation in hypertensive patients: nicardipine versus diltiazem	藤井善隆	取手協同病院	田中弘彦	取手協同病院	齋藤祐司	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院					1995	挿管反応				全科		37
C	23	○		○				○	Canadian Journal of Anesthesia	Post-tetanic burst count: a stimulating pattern for profound neuromuscular blockade	齋藤祐司	東京医科歯科大学医学部附属病院	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院					1995							
C	24	○		○				○	Canadian Journal of Anesthesia	Amrinone improves contractility of fatigued diaphragm in dogs	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院							1995	犬					36	
C	25	○		○				○	Journal of Anesthesia	The dose-response relationship of amrinone in increasing the contractility of fatigued diaphragm in dogs	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院									1995	犬	アムリノン				16	
C	26	○		○				○	Journal of Anesthesia	Effects of nicardipine on diaphragmatic fatigue in the dog: The relationship between dosage and fatigability	藤井善隆	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院									1995	犬	ニカルジピン				24	

【資料 3 - 2】

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	27	○		○			RCTDB	○	Canadian Journal of Anesthesia	Antiemetic efficacy of granisetron and metoclopramide in children undergoing ophthalmic or ENT surgery	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院							1996	PONV	グラニセトロン	メトクロプラマイド		小児斜視・扁摘		70
B	28	○		○			RCTDB	○	Canadian Journal of Anesthesia	Granisetron and dexamethasone provide more improved prevention of postoperative emesis than granisetron alone in children	藤井善隆	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1996	PONV	グラニセトロン	デキサメサゾン		小児斜視・扁摘		60
B	29	○		○			RCTDB	○	Canadian Journal of Anesthesia	Antiemetic effects of granisetron on postoperative nausea and vomiting in patients with and without motion sickness	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院							1996	PONV	グラニセトロン			婦人科大手術		110
B	30	○		○			RCTDB	○	Canadian Journal of Anesthesia	Granisetron reduces vomiting after strabismus surgery and tonsillectomy in children	藤井善隆	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1996	PONV	グラニセトロン			小児斜視・扁摘		50
B	31	○		○			RCTDB	○	Canadian Journal of Anesthesia	Effective dose of granisetron for preventing postoperative emesis in children	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院							1996	PONV	グラニセトロン			小児斜視・扁摘		80
C	32	○		○				○	Anaesthesia and Intensive Care	Intraoperative ventilation with air and oxygen during laparoscopic cholecystectomy decreases the degree of postoperative hypoxaemia	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	東京医科歯科大学医学部附属病院							1996	低酸素				胆摘		30
C	33	○		○				○	Journal of Anesthesia	Dibutyryl cyclic AMP increases the contractility of fatigued diaphragm in dogs	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院							1996	犬	DBCAMP				36	
C	34	○		○				○	Journal of Anesthesia	Dobutamine increases contractility of fatigued diaphragm in dogs: The relationship between dose and diaphragmatic contractility	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	東京医科歯科大学医学部附属病院									1996	犬	ドブタミン				16	
B	35	○		○			RCTDB	○	Anesthesia and Analgesia	The effects of dexamethasone on antiemetics in female patients undergoing gynecologic surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	デキサメサゾン			婦人科大手術		270
B	36	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Granisetron reduces incidence of nausea and vomiting after breast surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	グラニセトロン			乳がん		50
B	37	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prevention of PONV with granisetron, droperidol and metoclopramide in female patients with history of motion sickness	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1997	PONV	グラニセトロン	ドロペリドール	メトクロプラマイド	婦人科大手術		120
B	38	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prophylactic antiemetic efficacy of granisetron in patients with and without previous postoperative emesis	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	グラニセトロン			婦人科大手術		90
B	39	○		○			RCTDB	○	Canadian Journal of Anesthesia	Granisetron reduces postoperative nausea and vomiting throughout menstrual cycle	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	グラニセトロン			婦人科大手術		120
B	40	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Effective dose of granisetron in the reduction of nausea and vomiting after breast surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	グラニセトロン			乳がん		120
B	41	○		○			RCTDB	○	Canadian Journal of Anesthesia	Granisetron reduces the incidence and severity of nausea and vomiting after laparoscopic cholecystectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1997	PONV	グラニセトロン			胆摘		80
B	42	○		○			RCTDB	○	British Journal of Anaesthesia	Granisetron reduces the incidence of nausea and vomiting after middle ear surgery	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1997	PONV	グラニセトロン			中耳		60
B	43	○		○				○	Canadian Journal of Anesthesia	Cardiovascular responses to tracheal extubation or LMA removal in normotensive and hypertensive patients	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1997	抜管反応	LMA			整形四肢		80
C	44	○		○				○	Journal of Anesthesia	Nicardipine inhibits amrinone-enhanced contractility in fatigued diaphragm	藤井善隆	東京医科歯科大学医学部附属病院	豊岡秀訓	筑波大学附属病院									1997	犬	ニカルジピン	アムリノン			20	
C	45	○		○					Anesthesia and Resuscitation = 麻酔と蘇生	Dopamine enhances contractility of fatigued diaphragm in anestheized dogs: Dose effects on strength of contraction	藤井善隆												1997	犬					20	
C	46	○		○					Anesthesia and Resuscitation = 麻酔と蘇生	Dose-response effect of dibutyryl cyclic AMP on contractility in fatigued diaphragm	藤井善隆												1997	犬					16	
B	47	○		○			RCTDB	○	British Journal of Anaesthesia	Oral granisetron prevents postoperative vomiting in children	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン			小児扁摘		160
B	48	○		○			RCTDB	○	British Journal of Anaesthesia	Granisetron-droperidol combination for the prevention of postoperative nausea and vomiting in female patients undergoing breast surgery	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	ドロペリドール		乳がん		150
B	49	○		○			RCTDB	○	Anesthesia and Analgesia	A granisetron-droperidol combination prevents postoperative vomiting in children	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	ドロペリドール		小児扁摘		180
B	50	○		○			RCTDB	○	British Journal of Anaesthesia	Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	デキサメサゾン		中耳		120
B	51	○		○			RCTDB	○	Anaesthesia	Prophylactic anti-emetic therapy with granisetron, droperidol and metoclopramide in female patients undergoing middle ear surgery	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	ドロペリドール	メトクロプラマイド	中耳		180
B	52	○		○			RCTDB	○	Anesthesia and Analgesia	Prophylactic oral antiemetics for preventing postoperative nausea and vomiting: granisetron versus domperidone	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン	ドンペリドン		婦人科大手術		100

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	**53**	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Prevention of nausea and vomiting with granisetron, droperidol and metoclopramide during and after spinal anaesthesia for caesarean section: a randomised, double-blind, placebo-	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1998	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	帝切		120
B	**54**	○		○			RCTDB	○	British Journal of Anaesthesia	Granisetron in the prevention of nausea and vomiting after middle-ear surgery: a dose-ranging study	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン			中耳		120
B	**55**	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Preoperative oral granisetron prevents postoperative nausea and vomiting	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1998	PONV	グラニセトロン			婦人科大手術		120
B	**56**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prophylactic antiemetic therapy with granisetron-droperidol combination in patients undergoing laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン	ドロペリドール		女性胆摘		150
B	**57**	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Prevention of nausea and vomiting in female patients undergoing breast surgery: a comparison with granisetron, droperidol, metoclopramide and placebo	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1998	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	乳がん		120
B	**58**	○		○			RCTDB	○	Anesthesia and Analgesia	Prevention of postoperative nausea and vomiting with a combination of granisetron and droperidol	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	ドロペリドール		婦人科大手術		150
B	**59**	○		○			RCTDB	○	Pediatric Anesthesia	Comparison of granisetron and droperidol in the prevention of vomiting after strabismus surgery or tonsillectomy in children	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン	ドロペリドール		小児扁摘斜視		80
B	**60**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prevention of PONV with granisetron, droperidol or metoclopramide in patients with postoperative emesis	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン	メトクロプラミド	ドロペリドール	婦人科大手術		90
B	**61**	○		○			RCTDB	○	European Journal of Anaesthesiology	Anti-emetic efficacy of prophylactic granisetron, droperidol and metoclopramide in the prevention of nausea and vomiting after laparoscopic	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	女性胆摘		120
B	**62**	○		○			RCTDB	○	Pediatric Anesthesia	Prophylactic therapy with granisetron in the prevention of vomiting after paediatric surgery: a randomised, double-blind comparison with droperidol and metoclopramide	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1998	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	小児体表		100
B	**63**	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Granisetron prevents nausea and vomiting during spinal anaesthesia for caesarean section	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1998	PONV	グラニセトロン			帝切		100
B	**64**	○		○			RCTDB	○	Acta Anaesthesiologica Scandinavica	Prophylactic antiemetic therapy with granisetron-dexamethasone combination in women undergoing breast surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1998	PONV	グラニセトロン	デキサメサゾン		乳がん		135
B	**65**	○		○			RCTDB	○	British Journal of Anaesthesia	Prophylactic antiemetic therapy with granisetron in women undergoing thyroidectomy	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン			甲状腺		100
B	**66**	○		○			RCTDB	○	European Journal of Anaesthesiology	Effective dose of granisetron for the prevention of post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	PONV	グラニセトロン			女性胆摘		120
B	**67**	○		○			RCTDB	○	British Journal of Anaesthesia	Prevention of postoperative nausea and vomiting in female patients during menstruation: comparison of droperidol, metoclopramide and granisetron	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	女性全科		120
C	**68**	○		○				○	Anaesthesia	Recovery of post-tetanic count and train-of-four responses at the great toe and thumb	齋藤祐司	東京医科歯科大学医学部附属病院	藤井善隆	筑波大学附属病院	Takahashi K	東京医科歯科大学医学部附属病院	槇田浩史	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	天羽敬祐	東京医科歯科大学医学部附属病院	1998							
B	**69**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Calcium channel blockers attenuate cardiovascular responses to tracheal extubation in hypertensive patients	藤井善隆	筑波大学附属病院	Kihara Shinichi	筑波大学附属病院	高橋伸二	筑波学園病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院			1998	挿管反応				整形外科		60
C	**70**	○		○				○	European Journal of Anaesthesiology	Post-tetanic burst count and train-of-four during recovery from vecuronium-induced intense neuromuscular block under different types of anaesthesia	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	藤井善隆	筑波大学附属病院	槇田浩史	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院			1998							
C	**71**	○		○				○	Acta Anaesthesiologica Scandinavica	Modified double burst stimulation at varying stimulating currents	齋藤祐司	東京医科歯科大学医学部附属病院	藤井善隆	筑波大学附属病院	槇田浩史	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	天羽敬祐	東京医科歯科大学医学部附属病院			1998							
B	**72**	○		○				○	Canadian Journal of Anesthesia	Cardiovascular responses to tracheal extubation or LMA removal in children	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1998	挿管反応				小児LMA		60
B	**73**	○		○			RCT	○	European Journal of Anaesthesiology	Efficacy of thoracic epidural analgesia following laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	田中弘彦	取手協同病院							1998	術後痛	硬麻			男女胆摘		44
B	**74**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Diltiazem-lidocaine combination for the attenuation of cardiovascular responses to tracheal intubation in hypertensive patients	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	高橋伸二	筑波学園病院	豊岡秀訓	筑波大学附属病院					1998	挿管反応	ジルチアゼム	リドカイン		全科高血圧		60
C	**75**	○		○				○	European Journal of Anaesthesiology	Accelographic and mechanical post-tetanic count and train-of-four ratio assessed at the great toe	齋藤祐司	取手協同病院	藤井善隆	筑波大学附属病院	Ueki M	東京医科歯科大学医学部附属病院	槇田浩史	東京医科歯科大学医学部附属病院	天羽敬祐	東京医科歯科大学医学部附属病院			1998							
C	**76**	○		○				○	Anesthesia and Analgesia	The effects of milrinone and its mechanism in the fatigued diaphragm in dogs	藤井善隆	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							1998	犬					34	
B	**77**	○		○			RCTDB	○	Anesthesia and Analgesia	Comparison of ramosetron and granisetron for preventing postoperative nausea and vomiting after gynecologic surgery	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ラモセトロン		婦人科大手術		120
B	**78**	○		○			RCTDB	○	European Journal of Anaesthesiology	Prophylactic therapy with combined granisetron and dexamethasone for the prevention of post-operative vomiting in children	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	デキサメサゾン		小児ヘルニア包茎		150

【資料 3 - 4】

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	**79**	○		○			RCTDB	○	European Journal of Anaesthesiology	Anti-emetic efficacy of prophylactic granisetron compared with perphenazine for the prevention of postoperative vomiting in children	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ペルフェナジン		小児扁摘		90
B	**80**	○		○			RCTDB	○	Journal of Clinical Anesthesia	Combination of granisetron and droperidol in the prevention of nausea and vomiting after middle ear surgery	藤井善隆	取手協同病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ドロペリドール		男女中耳		150
B	**81**	○		○			RCTDB	○	European Journal of Anaesthesiology	Granisetron reduces post-operative vomiting in children: a dose-ranging study	藤井善隆	取手協同病院	田中弘彦	取手協同病院									1999	PONV	グラニセトロン			小児ヘルニア包茎		120
B	**82**	○		○			RCTDB	○	Anesthesia and Analgesia	Granisetron/dexamethasone combination for reducing nausea and vomiting during and after spinal anesthesia for cesarean section	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	デキサメサゾン		腰麻帝切		120
B	**83**	○		○			RCTDB	○	Anesthesia and Analgesia	Preoperative oral antiemetics for reducing postoperative vomiting after tonsillectomy in children: granisetron versus perphenazine	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ペルフェナジン		小児扁摘		100
B	**84**	○		○			RCTDB	○	Pediatric Anesthesia	Combination of granisetron and droperidol for the prevention of vomiting after paediatric strabismus surgery	藤井善隆	筑波大学附属病院	齋藤祐司	東京医科歯科大学医学部附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ドロペリドール		小児斜視		120
B	**85**	○		○			RCTDB	○	Laryngoscope	Granisetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting after thyroidectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							1999	PONV	グラニセトロン	ドロペリドール	メトクロプラマイド	女性甲状腺		120
B	**86**	○		○			RCTDB	○	European Journal of Anaesthesiology	Prevention of post-operative nausea and vomiting with combined granisetron and droperidol in women undergoing thyroidectomy	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン	ドロペリドール		女性甲状腺		180
B	**87**	○		○			RCTDB	○	Laryngoscope	Prevention of nausea and vomiting after middle ear surgery: granisetron versus ramosetron	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							1999	PONV	グラニセトロン	ラモセトロン		男女中耳		100
B	**88**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Ramosetron vs granisetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	ラモセトロン	グラニセトロン		女性胆摘		80
B	**89**	○		○			RCTDB	○	Pediatric Anesthesia	Prevention of postoperative vomiting with granisetron in paediatric patients with and without a history of motion sickness	藤井善隆	筑波大学附属病院	齋藤祐司	筑波大学附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					1999	PONV	グラニセトロン			小児扁摘		120
B	**90**	○		○			RCTDB	○	Ophthalmology	Preoperative oral granisetron for the prevention of vomiting after strabismus surgery in children	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Ito Mutsuko	取手協同病院(眼科)							1999	PONV	グラニセトロン			小児斜視		120
B	**91**	○		○			RCTDB	○	Journal of Anesthesia	Prophylactic antiemetic therapy with droperidol in patients undergoing laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院							1999	PONV	ドロペリドール			男女胆摘		60
C	**92**	○		○				○	Anaesthesia	Relationship between stimulating current and accelerographic train-of-four response at the great toe	齋藤祐司	取手協同病院	鳴海豊	取手協同病院	藤井善隆	筑波大学附属病院	Ueki M	東京医科歯科大学医学部附属病院					1999							
C	**93**	○		○				○	British Journal of Anaesthesia	Tactile evaluation of fade of the train-of-four and double-burst stimulation using the anaesthetist's non-dominant hand	齋藤祐司	取手協同病院	鳴海豊	取手協同病院	藤井善隆	筑波大学附属病院	Ueki M	東京医科歯科大学医学部附属病院					1999							
C	**94**	○		○				○	British Journal of Anaesthesia	Post-tetanic count and train-of-four responses during neuromuscular block produced by vecuronium and infusion of nicardipine	齋藤祐司	取手協同病院	鳴海豊	取手協同病院	藤井善隆	筑波大学附属病院							1999							
B	**95**	○		○				○	Anaesthesia and Intensive Care	Blood flow velocity in the middle cerebral artery response to tourniquet release	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	Ishikawa E	筑波大学附属病院(脳神経外科)	Kato N	筑波大学附属病院(脳神経外科)					1999	中大脳動脈				整形四肢		30
C	**96**	○		○				○	British Journal of Anaesthesia	Electromyographic assessment of neuromuscular block at the gastrocnemius muscle	齋藤祐司	取手協同病院	鳴海豊	取手協同病院	藤井善隆	筑波大学附属病院	Ueki M	東京医科歯科大学医学部附属病院	槇田浩史	東京医科歯科大学医学部附属病院			1999							
C	**97**	○		○				○	Anesthesia and Analgesia	The ulnistatin-induced effect on neuromuscular block caused by vecuronium	齋藤祐司	取手協同病院	藤井善隆	筑波大学附属病院	大島勉	岐阜大学附属病院							1999							
B	**98**	○		○			RCTDB	○	Canadian Journal of Anesthesia	Combined diltiazem and lidocaine reduces cardiovascular responses to tracheal extubation and anesthesia emergence in hypertensive patients	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院					1999	抜管反応	ジルチアゼム			高血圧整形四肢		60
B	**99**	○		○				○	Anesthesia and Analgesia	The effect of olprinone compared with milrinone on diaphragmatic muscle function in dogs	藤井善隆	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							1999	犬					40	
B	**100**	○		○				○	Anesthesia and Analgesia	Propofol decreases diaphragmatic contractility in dogs	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院					1999	犬					30	
A	**101**	○		○				○	Canadian Journal of Anesthesia	Landiolol decreases a dysrhythmogenic dose of epinephrine in dogs during halothane anesthesia	高橋伸二	筑波大学附属病院	藤井善隆	筑波大学附属病院	Inomata Shin ichi	筑波大学附属病院	宮部雅幸	筑波大学附属病院	豊岡秀訓	筑波大学附属病院			1999	犬					10	10
B	**102**	○		○				○	European Journal of Anaesthesiology	Milrinone enhances the contractility of fatigued diaphragm in dogs:a dose-ranging study.	藤井善隆	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							1999	犬					24	
B	**103**	○		○				○	Anaesthesia and Intensive Care	Protection from diaphragmatic fatigue by nitric oxide synthase inhibitor in dogs.	藤井善隆	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							1999	犬					26	
B	**104**	○		○			RCTDB	○	European Journal of Anaesthesiology	Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					2000	PONV	グラニセトロン	デキサメサゾン		男女胆摘		120

【資料 3 - 5】

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	105	○		○			RCTDB	○	Anaesthesia and Intensive Care	Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after thyroidectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							2000	PONV	グラニセトロン	デキサメサゾン		女性甲状腺		130
B	106	○		○			RCTDB	○	Anesthesia and Analgesia	Ramosetron for preventing postoperative nausea and vomiting in women undergoing gynecological surgery	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					2000	PONV	ラモセトロン			婦人科大手術		120
B	107	○		○			RCTDB	○	American Journal of Obstetrics and Gynecology	Granisetron, droperidol, and metoclopramide for the treatment of established postoperative nausea and vomiting in women undergoing	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Somekawa Yoshiaki	取手協同病院(産婦人科)							2000	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	婦人科大手術		120
B	108	○		○			RCTDB	○	British Journal of Surgery	Randomised clinical trial of granisetron, droperidol and metoclopramide for the treatment of nausea and vomiting after laparoscopic cholecystectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)							2000	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	男女胆摘		120
B	109	○		○			RCTDB	○	Anaesthesia and Intensive Care	Subhypnotic dose of propofol for the prevention of nausea and vomiting during spinal anaesthesia for caesarean section	沼崎満子	筑波大学附属病院	藤井善隆	筑波大学附属病院									2000	血管痛				腰麻帝切		60
B	110	○		○			RCTDB	○	Pediatric Anesthesia	Pretreatment with oral clonidine attenuates cardiovascular responses to tracheal extubation	藤井善隆	筑波大学附属病院	齋藤祐司	取手協同病院	田中弘彦	取手協同病院	豊岡秀訓	筑波大学附属病院					2000	抜管反応	クロニジン	ジアゼパム		小児ヘルニア包茎		50
B	111	○		○				○	Anesthesia and Analgesia	The effect of sedative drugs on diaphragmatic contractility in dogs: propofol versus midazolam	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院					2000	犬					30	
A	112	○		○				○	Canadian Journal of Anesthesia	Modifications of the hemodynamic consequences of theophylline intoxication with landiolol in halothane-anesthetized dogs	高橋伸二	筑波大学附属病院	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	Inomata Shin ichi	筑波大学附属病院	宮部雅幸	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	2000	犬					34	
C	113	○		○				○	Canadian Journal of Anesthesia	Effect of xenon on diaphragmatic contractility in dogs	星拓男	筑波大学附属病院	藤井善隆	筑波大学附属病院	高橋伸二	筑波大学附属病院	豊岡秀訓	筑波大学附属病院					2000	犬					21	
B	114	○		○				○	Canadian Journal of Anesthesia	Different effects of olprinone on contractility in nonfatigued and fatigued diaphragm in dogs	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院									2000	犬					36	
B	115	○		○			RCTDB	○	Archives of Otolaryngology Head and Neck Surgery	Prevention of postoperative nausea and vomiting with antiemetics in patients undergoing middle ear surgery: comparison of a small dose of propofol with droperidol or metoclopramide	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							2001	PONV	ドロペリドール	メトクロプラミド		中耳		90
B	116	○		○			RCTDB	○	Otolaryngology - Head and Neck Surgery	Small doses of propofol, droperidol, and metoclopramide for the prevention of postoperative nausea and vomiting after thyroidectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							2001	PONV	ドロペリドール	メトクロプラミド		甲状腺		90
B	117	○		○			RCTDB	○	Journal of Pediatric Surgery	Comparison of granisetron, droperidol, and metoclopramide for prevention of postoperative vomiting in children with a history of motion sickness undergoing tonsillectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2001	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	小児扁摘		90
B	118	○		○			RCTDB	○	European Journal of Surgery	Preoperative oral granisetron for the prevention of postoperative nausea and vomiting after breast surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)							2001	PONV	グラニセトロン			乳がん		100
B	119	○		○			RCTDB	○	Laryngoscope	Prevention of vomiting after tonsillectomy in children: granisetron versus ramosetron	藤井善隆	取手協同病院	齋藤祐司	取手協同病院	Kobayashi Noriaki	取手協同病院(耳鼻咽喉科)							2001	PONV	グラニセトロン	ラモセトロン		小児扁摘		90
B	120	○		○			RCTDB	○	British Journal of Ophthalmology	Ramosetron compared with granisetron for the prevention of vomiting following strabismus surgery in children	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Ito Mutsuko	取手協同病院(眼科)							2001	PONV	ラモセトロン	グラニセトロン		小児斜視		80
B	121	○		○			RCTDB	○	Archives of Surgery	Prophylaxis with oral granisetron for the prevention of nausea and vomiting after laparoscopic cholecystectomy: a prospective randomised study	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)							2001	PONV	グラニセトロン			男女胆摘		120
B	122	○		○			RCTDB	○	Pediatric Anesthesia	The efficacy of oral clonidine premedication in the prevention of postoperative vomiting in children following strabismus surgery	半田冨美(筒井冨美)	兵庫県立こども病院	藤井善隆	筑波大学附属病院									2001	PONV	クロニジン			斜視		60
C	123	○		○				○	Canadian Journal of Anesthesia	Nicorandil accelerates recovery of neuromuscular block caused by vecuronium	齋藤祐司	福島医科大学病院	Kaneda Koh	取手協同病院	藤井善隆	筑波大学附属病院	大島勉	岐阜大学附属病院					2001	不要						
B	124	○		○				○	Anesthesia and Analgesia	Colforsin daropate improves contractility in fatigued canine diaphragm	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2001	犬					32	
B	125	○		○				○	Anesthesia and Analgesia	Dose-response characteristics of midazolam for reducing diaphragmatic contractility	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院					2001	犬					24	
B	126	○		○				○	Anesthesia and Analgesia	The dose-range effects of propofol on the contractility of fatigued diaphragm in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2001	犬					24	
B	127	○		○				○	British Journal of Anaesthesia	Midazolam versus propofol for reducing contractility of fatigued canine diaphragm	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院									2001	犬					30	
B	128	○		○			RCTDB	○	Anesthesia and Resuscitation = 麻酔と蘇生	Diltiazem or verapamil attenuates cardiovascular responses to tracheal intubation in hypertensive patients	藤井善隆	筑波大学附属病院											2001	挿管反応	ジルチアゼム	ベラパミル		全科高血圧		45
B	129	○		○			RCTDB	○	Obstetrics and Gynecology	Dexamethasone for the prevention of nausea and vomiting after dilatation and curettage: a randomised controlled trial	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院									2002	PONV	デキサメサゾン			中絶		120
B	130	○		○			RCTDB	○	Pediatric Anesthesia	Preoperative oral granisetron for the prevention of vomiting following paediatric surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2002	PONV	グラニセトロン			小児		100

【資料 3 - 6】

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	131	○		○			RCTDB	○	European Journal of Surgery	Prophylaxis of nausea and vomiting after laparoscopic cholecystectomy with ramosetron: Randomised controlled trial	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	田中弘彦	取手協同病院							2002	PONV	ラモセトロン			胆摘		100
B	132	○		○			RCTDB	○	Clinical Therapeutics	Comparison of granisetron and ramosetron for the prevention of nausea and vomiting after thyroidectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2002	PONV	グラニセトロン	ラモセトロン		甲状腺		80
B	133	○		○			RCTDB	○	Journal of Oral and Maxillofacial Surgery	Small dose of propofol for preventing nausea and vomiting after third molar extraction	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	Nakano Mayu	筑波大学附属病院(口頭・顎顔面外科)							2002	PONV	プロポフォール			歯科抜歯		90
B	134	○		○			RCTDB	○	Clinical Therapeutics	Double-blind, placebo-controlled, dose-ranging study of ramosetron for the prevention of nausea and vomiting after thyroidectomy	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2002	PONV	ラモセトロン			甲状腺		80
B	135	○		○			RCTDB	○	Ophthalmologica	Treatment of vomiting after paediatric strabismus surgery with granisetron, droperidol, and metoclopramide	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Ito Mutsuko	取手協同病院(眼科)							2002	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	小児斜視		120
B	136	○		○			RCTDB	○	Obstetrics and Gynecology	Dose-range effects of propofol for reducing emetic symptoms during cesarean delivery	藤井善隆	筑波大学附属病院	沼崎満子	筑波大学附属病院									2002	PONV	プロポフォール			帝切		80
B	137	○		○				○	Anesthesia and Analgesia	The dose-related efficacy of diltiazem for enhancing diaphragmatic fatigability in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2002	犬					24	
B	138	○		○				○	Anesthesia and Analgesia	Flumazenil recovers diaphragm muscle dysfunction caused by midazolam in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2002	犬					24	
C	139	○		○				○	British Journal of Anaesthesia	Inhaled olprinone improves contractility of fatigued canine diaphragm	上村明	筑波大学附属病院	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2002	犬					24	
B	140	○		○				○	Canadian Journal of Anesthesia	High-dose colforsin daropate increases diaphragmatic contractility in dogs	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院									2002	犬					24	
C	141	○		○				○	Acta Anaesthesiologica Scandinavica	Comparative effects of xenon and nitrous oxide on diaphragmatic contractility in dogs.	星拓男	筑波大学附属病院	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2002	犬					21	
B	142	○		○			RCTDB	○	Clinical Drug Investigation	Prevention of nausea and vomiting with ramosetron after total hip replacement	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2003	PONV	ラモセトロン			股関節置換		80
B	143	○		○			RCTDB	○	Clinical Therapeutics	Randomised, double-blind, placebo-controlled, dose-finding study of the antiemetic effects and tolerability of ramosetron in adults undergoing middle ear surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2003	PONV	ラモセトロン			中耳		100
B	144	○		○			RCTDB	○	Canadian Journal of Anesthesia	Prevention of nausea and vomiting after dental surgery: a comparison of small doses of propofol, droperidol, and metoclopramide	Nakano Mayu	筑波大学附属病院	藤井善隆	筑波大学附属病院									2003	PONV	ドロペリドール	メトクロプラミド		歯科口腔外科		90
B	145	○		○			RCTDB	○	Current Therapeutic Research	A randomised, double-blind comparison of granisetron alone and combined with dexamethasone for post-laparoscopic cholecystectomy emetic symptoms	藤井善隆	筑波大学附属病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)							2003	PONV	グラニセトロン	デキサメサゾン		胆摘		100
B	146	○		○			RCTDB	○	Clinical Therapeutics	A comparison of granisetron, droperidol, and metoclopramide in the treatment of established nausea and vomiting after breast surgery: a double-blind, randomised, controlled trial	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)							2003	PONV	グラニセトロン	ドロペリドール	メトクロプラミド	乳がん		75
B	147	○		○			RCTDB	○	Clinical Therapeutics	Granisetron versus granisetron/dexamethasone combination for the treatment of nausea, retching, and vomiting after major gynecologic surgery: a randomised, double-blind study	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2003	PONV	グラニセトロン	デキサメサゾン		婦人科大手術		120
B	148	○		○				○	Anesthesia and Analgesia	Midazolam-induced muscle dysfunction and its recovery in fatigued diaphragm in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2003	犬					24	
B	149	○		○				○	Anesthesia and Analgesia	The effect of inhaled colforsin daropate on contractility of fatigued diaphragm in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院							2003	犬					24	
A	150	○		○				○	Canadian Journal of Anesthesia	Milrinone attenuates the negative inotropic effects of landiolol in halothane-anesthetized dogs	高橋伸二	筑波大学附属病院	藤井善隆	筑波大学附属病院	星拓男	筑波大学附属病院	上村明	筑波大学附属病院	宮部雅幸	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	2003	犬					18	
B	151	○		○				○	European Journal of Anaesthesiology	Effects of diltiazem compared with nicardipine on diaphragmatic fatigability in vivo	藤井善隆	筑波大学附属病院											2003	犬					16	
C	152	○		○				○	Anesthesia and Analgesia	Olprinone for the treatment, but not prevention, of fatigue-induced changes in guinea-pig diaphragmatic contractility	上村明	筑波大学附属病院	藤井善隆	筑波大学附属病院	豊岡秀訓	筑波大学附属病院	鈴木ｾﾂｺ	筑波大学附属病院(研究所)	Sawada Kohei	筑波大学附属病院(研究所)	Adachi Hideyuki	筑波大学附属病院(研究所)	2003	モルモット					21	
B	153	○		○			RCTDB	○	Clinical Therapeutics	Results of a prospective, randomized, double-blind, placebo-controlled, dose-ranging trial to demonstrate the effective dose of ramosetron for the prevention of vomiting after tonsillectomy in children	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2003	PONV	ラモセトロン			小児扁摘		80
B	154	○		○			RCTDB	○	Journal of Clinical Anesthesia	Reduction of emetic symptoms during Cesarean delivery with antiemetics: propofol at subhypnotic dose versus traditional antiemetics	沼崎満子	筑波大学附属病院	藤井善隆	筑波大学附属病院									2003	PONV	プロポフォール	ドロペリドール	メトクロプラミド	帝切		100
B	155		○	○					麻酔	ジルチアゼムの横隔膜収縮力及び横隔膜筋電図に及ぼす影響	藤井善隆	筑波大学 臨床医学系麻酔科											2003	犬	ジルチアゼム				18	

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	156	○		○					Current Therapeutic Research Clinical and Experimental	Treatment of Diaphragmatic Fatigue with Inhaled Aminophylline Therapy in an Experimental Canine Model: An Open-Label, Dose-Ranging, Pharmacologic	藤井善隆												2003	犬					28	
B	157	○		○			RCTDB		Anesthesia and Resuscitation = 麻酔と蘇生	Small dose of propofol for preventing emetic episodes in women undergoing mastectomy	上村明	筑波大学附属病院	藤井善隆									2003	PONV				乳がん		40
B	158	○		○					Anesthesia and Resuscitation = 麻酔と蘇生	Supplemental Oxygen for the Prevention of Diaphragmatic Fatigability in Pentobarbital-Anesthetized Dogs	上村明		藤井善隆									2003	犬					18	
B	159	○		○			RCTDB	○	International Journal of Obstetric Anesthesia	A randomised, double-blind, placebo-controlled trial of ramosetron for preventing nausea and vomiting during termination of pregnancy	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Somekawa Yoshiaki	取手協同病院(産婦人科)					2004	PONV	ラモセトロン			中絶		80
B	160	○		○			RCTDB	○	American Journal of Therapeutics	Benefits and risks of granisetron versus ramosetron for nausea and vomiting after breast surgery: a randomised, double-blinded, placebo-controlled trial	藤井善隆	筑波大学附属病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)					2004	PONV	グラニセトロン	ラモセトロン		乳癌		90
B	161	○		○			RCTDB	○	Current Therapeutic Research	Treatment of postoperative emetic symptoms with granisetron in women undergoing abdominal hysterectomy: a randomised, double-blind, placebo-controlled, dose-ranging study	藤井善隆	筑波大学附属病院	田中弘彦	取手協同病院	Somekawa Yoshiaki	取手協同病院(産婦人科)					2004	PONV	グラニセトロン			子宮摘出		100
B	162	○		○			RCTDB	○	Clinical Therapeutics	Effects of granisetron in the treatment of nausea and vomiting after laparoscopic cholecystectomy: a dose-ranging study	藤井善隆	筑波大学附属病院	田中弘彦	取手協同病院	Kawasaki Tsuneo	取手協同病院(外科)					2004	PONV	グラニセトロン			胆摘		100
B	163	○		○			RCTDB	○	Clinical Therapeutics	Randomised, double-blind comparison of subhypnotic-dose propofol alone and combined with dexamethasone for emesis in parturients undergoing cesarean	藤井善隆	筑波大学附属病院	沼崎満子	筑波大学大学院（人間総合科学研究科）							2004	PONV	デキサメサゾン			帝切		120
B	164	○		○			RCTDB	○	Anaesthesia and Intensive Care	Effect of metoclopramide on pain on injection of propofol	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院								2004	血管痛	メトクロプラマイド			全科		100
B	165	○		○				○	Canadian Journal of Anesthesia	Pretreatment with flurbiprofen axetil and venous occlusion to reduce pain during injection of propofol	藤井善隆	筑波大学附属病院										2004	血管痛	ロピオン			女性円錐切除		40
B	166	○		○				○	Anesthesia and Analgesia	The recovery profile of reduced diaphragmatic contractility induced by propofol in dogs	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院	豊岡秀訓	筑波大学附属病院						2004	犬					28	
B	167	○		○			RCTDB	○	Clinical Drug Investigation	Reduction of propofol-induced pain through pretreatment with lidocaine and/or flurbiprofen	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院								2004	血管痛	ロピオン			形成		120
B	168		○	○					Anesthesia and Resuscitation = 麻酔と蘇生	乳房切除術患者の術後悪心・嘔吐に対する少量のプロポフォールの制吐効果	萩谷圭一	筑波大学附属病院	藤井善隆	筑波大学大学院								2004	PONV	プロポフォール			乳がん		80
B	169	○		○					Pulmonary Pharmacology and Therapeutics	Comparative effects of dopamine and dobutamine on hypercapnic depression of diaphragmatic contractility in dogs	藤井善隆											2004	犬					30	
B	170	○		○					Pulmonary Pharmacology and Therapeutics	Inhaled milrinone for the improvement of contractility of fatigued diaphragm in dogs: A dose-ranging study	藤井善隆											2004	犬					28	
B	171	○		○					Anesthesia and Resuscitation = 麻酔と蘇生	Aerosolized isoproterenol increases contractility of fatigued diaphragm in dogs	沼崎満子		藤井善隆									2004	犬					21	
B	172	○		○			RCTDB	○	Archives of Ophthalmology	A randomised clinical trial of a single dose of ramosetron for the prevention of vomiting after strabismus surgery in children	藤井善隆	取手協同病院	田中弘彦	取手協同病院	Ito Mutsuko	取手協同病院(眼科)					2005	PONV	ラモセトロン			小児斜視		80
B	173	○		○			RCTDB	○	Clinical Therapeutics	Effects of dexamethasone in preventing postoperative emetic symptoms after total knee replacement surgery: a prospective, randomised, double-blind, placebo-controlled trial in adults	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院							2005	PONV	デキサメサゾン			膝関節置換		80
B	174	○		○			RCTDB	○	Canadian Journal of Anesthesia	Antiemetic efficacy of propofol at small doses for reducing nausea and vomiting following thyroidectomy	沼崎満子	筑波大学附属病院	藤井善隆	筑波大学附属病院							2005	PONV	ロピオン	プロポフォール		こうじょうせん		80
B	175	○		○			RCTDB	○	Journal of Clinical Anesthesia	Reduction of postoperative emetic episodes and analgesic requirements with dexamethasone in patients scheduled for dental surgery	沼崎満子	筑波大学附属病院	藤井善隆	筑波大学附属病院							2005	PONV	デキサメサゾン			歯科抜歯		120
B	176	○		○			RCTDB	○	Canadian Journal of Anesthesia	A lidocaine/metoclopramide combination decreases pain on injection of propofol	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院							2005	血管痛	メトクロプラマイド	リドカイン		形成		90
B	177	○		○			RCTDB	○	Clinical Therapeutics	Flurbiprofen axetil preceded by venous occlusion in the prevention of pain on propofol injection in the hand: a prospective, randomized, double-blind, vehicle-controlled, dose-finding study in Japanese adult surgical patients	藤井善隆	筑波大学附属病院	志賀由佳	筑波大学附属病院							2005	血管痛	ロピオン			全科		120
B	178	○		○			RCTDB	○	Clinical Drug Investigation	Efficacy of lignocaine plus ketamine at different doses in the prevention of pain due to propofol injection	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院							2005	血管痛		ケタミン		婦人科ラパロ		120
B	179	○		○			RCTDB	○	Anesthesia and Resuscitation = 麻酔と蘇生	Effective dose of propofol at small dose for preventing postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy	藤井善隆	筑波大学大学院（人間総合科学研究科）									2005	PONV	プロポフォール			胆摘		80
B	180	○		○					Current Therapeutic Research Clinical and Experimental	Effects of diazepam on diaphragmatic functionand recovery in pentobarbital-anesthetized dogs: An open-label, dose-finding, pharmacologic study	藤井善隆											2005	犬					24	

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	181	○		○					Anesthesia and Resuscitation = 麻酔と蘇生	Comparative antiemetic efficacy of small dose of propofol and metoclopramide for preventing nausea and vomiting after laparoscopic cholecystectomy	志賀由香		藤井善隆										2005	PONV				胆摘		30
B	182	○		○			RCTDB	○	Clinical Drug Investigation	Efficacy of granisetron for the treatment of postoperative nausea and vomiting in women undergoing breast surgery	藤井善隆	取手協同病院	田中弘彦	取手協同病院									2006	PONV	グラニセトロン			乳がん		100
B	183	○		○			RCTDB	○	Clinical Therapeutics	Influence of age on flurbiprofen axetil requirements for preventing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, vehicle-controlled, parallel group, dose-ranging study	藤井善隆	東邦大学医学部 麻酔科学第1講座	中山 Masahiro	筑波大学附属病院									2006	血管痛	ロピオン			全科		150
B	184	○		○			RCTDB	○	Clinical Drug Investigation	Age-related differences in metoclopramide requirement for pain on injection of propofol	藤井善隆	筑波大学附属病院	志賀由佳	筑波大学附属病院									2006	血管痛	メトクロプラマイド			全科		120
B	185	○		○			RCTDB	○	Journal of Clinical Anesthesia	Influence of aging on lidocaine requirements for pain on injection of propofol	藤井善隆	筑波大学附属病院	志賀由佳	筑波大学附属病院									2006	血管痛	リドカイン			全科		160
B	186	○		○				○	Anesthesia and Resuscitation = 麻酔と蘇生	Jiachiruzemu does not affect the force of contraction of the diaphragm and EMG fatigue.	藤井善隆	筑波大学大学院（人間総合科学研究科）	板倉美千代	牛久愛和総合病院									2006	犬	ジルチアゼム				10	
B	187	○		○				○	Anesthesia and Resuscitation = 麻酔と蘇生	No Beneficial Effect of Neostigmine Pretreatment on Diaphragmatic Fatigue in Pentobarbital-Anesthetized Dogs.	藤井善隆	東邦大学医学部 麻酔科学第1講座	上村明	筑波大学附属病院									2006	犬					21	
B	188	○		○					Current Therapeutic Research Clinical and Experimental	Olprinone/dopamine combination for improving diaphragmatic fatigue in pentobarbital-anesthetized dogs	藤井善隆												2006	犬					28	
B	189	○		○			RCTDB	○	Breast Journal	Reduction of postoperative nausea and vomiting and analgesic requirement with dexamethasone in women undergoing general anesthesia for mastectomy	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院									2007	PONV	デキサメサゾン			乳癌		94
B	190	○		○			RCTDB	○	Otolaryngology - Head and Neck Surgery	Efficacy of dexamethasone for reducing postoperative nausea and vomiting and analgesic requirements after thyroidectomy	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院（耳鼻咽喉科）									2007	PONV	デキサメサゾン			甲状腺		75
B	191	○		○			RCTDB	○	Clinical Therapeutics	Prevention of pain due to injection of propofol with iv administration of lidocaine 40mg + metoclopramide 2.5, 5, or 10mg or saline: a randomised, double-blind study in Japanese adult surgical patients	藤井善隆	東邦大学医学部 麻酔科学第1講座	中山 Masahiro	筑波大学附属病院									2007	血管痛	メトクロプラマイド	リドカイン		全科		240
B	192	○		○			RCTDB	○	British Journal of Oral and Maxillofacial Surgery	Propofol alone and combined with dexamethasone for the prevention of postoperative nausea and vomiting in adult Japanese patients having third molars extracted	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院	Nakano Mayu	筑波大学附属病院（口頭・顎顔面外科）						2007	PONV	デキサメサゾン	プロポフォール		口外（歯科抜歯？）		120
B	193	○		○				○	Anesthesia and Analgesia	The effects of different dobutamine infusion rates on hypercapnic depression of diaphragmatic contractility in pentobarbital-anesthetized dogs.	藤井善隆	筑波大学附属病院	上村明	筑波大学附属病院									2007	犬					24	雑種
B	194	○		○				○	Anesthesia and Resuscitation = 麻酔と蘇生	Effect of diaphragmatic electromyogram and force of contraction of the diaphragm flumazenil.	藤井善隆	東邦大学医学部 麻酔科学第1講座	上村明	筑波大学大学院（人間総合科学研究科）									2007	犬					8	雑種
B	195	○		○				○	Anesthesia and Resuscitation = 麻酔と蘇生	Low-Dose of Diazepam, but not Midazolam, Delays Recovery from Diaphragm Muscle Dysfunction in Dogs.	藤井善隆	東邦大学医学部 麻酔科学第1講座	上村明	筑波大学附属病院									2007	犬					18	雑種
B	196	○		○					Current Therapeutic Research Clinical and Experimental	Effects of milrinone and olprinone on hypercapnic depression of diaphragmatic contractility in pentobarbital-anesthetized dogs	藤井善隆		上村明										2007	犬					24	
B	197	○		○			RCTDB	○	International Journal of Gynecology and Obstetrics	Dexamethasone for reduction of nausea, vomiting and analgesic use after gynecological laparoscopic surgery	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院									2008	PONV	デキサメサゾン			婦人科		90
B	198	○		○			RCTDB	○	Clinical therapeutics	Comparison of propofol, droperidol, and metoclopramide for prophylaxis of postoperative nausea and vomiting after breast cancer surgery: a prospective, randomised, double-blind, placebo-controlled study in Japanese patients	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2008	PONV	ドロペリドール	メトクロプラマイド		乳がん		100
B	199	○		○			RCTDB	○	Surgical Endoscopy	Prevention of postoperative nausea and vomiting with a small dose of propofol alone and combined with dexamethasone in patients undergoing laparoscopic cholecystectomy: a prospective, randomised, double-blind study	藤井善隆	筑波大学附属病院	中山 Masahiro	筑波大学附属病院									2008	PONV	プロポフォール	デキサメサゾン		胆摘		120
B	200	○		○			RCTDB	○	Anesthesia and Resuscitation = 麻酔と蘇生	Supplemental oxygen prevents postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgery	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2008	PONV	酸素			婦人科腹腔鏡		60
B	201	○		○			RCTDB	○	Clinical Therapeutics	Comparison of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, parallel-group, placebo-controlled study	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2008	血管痛	メトクロプラマイド	ロピオン		全科		100
B	202	○		○					Current Therapeutic Research Clinical and Experimental	Dose-related effects of olprinone on hypercapnia-induced impairment of diaphragmatic contractility in pentobarbital-anesthetized dogs	藤井善隆		上村明										2008	犬					24	

判定	通番	英文論文	和文論文	原著	総説	症例報告	RCT	JointEIC調査対象	雑誌	タイトル	著者	著者所属	共著者1	共著者1所属	共著者2	共著者2所属	共著者3	共著者3所属	共著者4	共著者4所属	共著者5	共著者5所属	年	研究(テーマ)	薬剤1	薬剤2	薬剤3	対象	犬頭数	症例数
B	203	○		○			RCTDB	○	Clinical Therapeutics	Pretreatment with flurbiprofen axetil, flurbiprofen axetil preceded by venous occlusion, and a mixture of flurbiprofen axetil and propofol in reducing pain on injection of propofol in adult Japanese surgical patients: a prospective, randomized double-blin	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2009	血管痛	ロピオン			全科		150
B	204	○		○			RCTDB	○	International Journal of Gynecology and Obstetrics	Low-dose propofol propofol to prevent nausea and vomiting after laparoscopic surgery	藤井善隆	牛久愛和総合病院	板倉美千代	牛久愛和総合病院									2009	PONV	プロポフォール			婦人科腹腔鏡		90
B	205	○		○			RCTDB	○	Clinical Therapeutics	A comparison of pretreatment with fentanyl and lidocaine preceded by venous occlusion for reducing pain on injection of propofol: a prospective, randomized, double-blind, placebo-controlled study in adult Japanese surgical patients	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2009	血管痛	フェンタニル	リドカイン		全科		120
B	206	○		○					Methods and Findings in Experimental and Clinical Pharmacology	Dexamethasone for the reduction of postoperative nausea and vomiting and analgesic requirements after middle ear surgery in adult Japanese patients	藤井善隆		Nakayama M										2009	PONV				中耳	93	
B	207	○		○			RCTDB	○	Surgical Endoscopy	Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy	藤井善隆	牛久愛和総合病院	板倉美千代	牛久愛和総合病院									2010	PONV	デキサメサゾン			胆摘		90
B	208	○		○			RCTDB	○	Clinical Therapeutics	A prospective, randomized, double-blind, placebo-controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2010	PONV	ミダゾラム			婦人科		90
B	209	○		○				○	Anesthesia and Resuscitation = 麻酔と蘇生	Dopamine in a dose-dependent manner to improve the force of contraction of the diaphragm decreased by high CO2 blood.	藤井善隆	東邦大学医学部 麻酔科学第1講座	高橋伸二	筑波大学大学院(人間総合科学研究科)									2010	犬	ドーパミン				8	雑種
B	210	○		○					Current Therapeutic Research - Clinical and Experimental	Effects of dibutyryl cyclic adenosine monophosphate on hypercapnic depression of diaphragmatic contractility in pentobarbital-anesthetized dogs	藤井善隆		Uemura A										2010	犬					21	
B	211	○		○			RCTDB	○	Minerva Anestesiologica	Efficacy of the lidocaine / flurbiprofen axetil combination for reducing pain during the injection of propofol	藤井善隆	東邦大学医学部 麻酔科学第1講座	板倉美千代	牛久愛和総合病院									2011	血管痛	ロピオン			全科		100
B	212	○		○			RCTDB	○	Otolaryngology - Head and Neck Surgery	Antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy.	藤井善隆	牛久愛和総合病院	板倉美千代	牛久愛和総合病院									2011	PONV	ミダゾラム			甲状腺		90

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Correspondence

The analysis of 168 randomised controlled trials to test data integrity

I seriously read the Special Article by Dr Carlisle [1]. As is well known, Dr. Carlisle is interested in the area of peri-operative medicine [2]. Similarly, I am interested in this area and have made efforts to improve the postoperative outcomes of surgical patients. Additionally, we have provided information on diaphragm muscle dysfunction and its improvement in animal studies. However, this article by Carlisle can obviously be very damaging to me and I want to answer it seriously, but I am not a statistician. I can only offer a few elements of rebuttal at this point.

Postoperative nausea and vomiting (PONV) remains a common complication for surgical patients. In addition to patients' discomfort, the physical act of vomiting may increase the risk of aspiration, wound dehiscence, and delayed recovery and discharge times [3]. For the management of PONV in high-risk patients, we have evaluated the efficacy and safety of antiemetics, including serotonin receptor antagonists, droperidol, metoclopramide and others, as first reported by us in 1994 [4]. Factors affecting PONV include patients' characteristics, surgical procedure, anaesthetic technique and postoperative care [3]. Patient-related factors associated with increased PONV include age, female sex, obesity, a history of motion sickness and/or previous PONV, and menstruation. Increasing age during adulthood is associated with a decreased incidence of PONV. Considering these factors, most reports by us have excluded patients aged over 60 years, those who were obese, those with a history of motion sickness and/or previous PONV, and those who were menstruating. Being different from European and American nations, most Japanese people are middle-sized. Consequently, patients' characteristics would be comparable in our series of clinical investigations. In addition, middle-aged Japanese women suffer from specific diseases, such as uterine myoma, breast cancer and goitre. Difference in diet, level of stress, etc can certainly produce a bizarre distribution of data specific to Japanese people. We cannot select the patients of our studies as broadly as we would want to.

As described in Kranke et al.'s letter and my response [5], granisetron, classified as a serotonin receptor antagonist, lacks the sedative, dysphoric and extrapyramidal symptoms associated with non-serotonin receptor antagonists. It is known that mild headache is one of the adverse effects in patients receiving granisetron. As mentioned in our published articles, trained nurses asked the patients about their conditions postoperatively. According to these results, in our manuscripts, its incidence was verified as approximately 10%. The researchers asked the patients if they experienced headache, dizziness and drowsiness, with only two possible answers (yes/no). This assessment might have caused the identical results regarding the incidence of postoperative adverse events. When analysing the degree of headache in detail, different results may have been obtained.

The diaphragm is the most important muscle in the respiratory pump. Since publishing our first laboratory report [6], we have studied the effects of several drugs, such as phospodiesterase-3 inhibitors, calcium channel blockades, benzodiazepines, and others, on diaphragmatic contractility in animals. All measure-

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ments (including haemodynamics, blood gas tensions, trans-diaphragmatic pressure and integrated activity of the diaphragm) and analyses of data obtained from the experiments were performed by myself and colleagues (co-authors), and this can be proved by them.

I understand that the tests by Dr. Carlisle are designed to uncover statistical anomalies based on very few assumptions about the data. I am not qualified to counter specific allegations concerning the 'central limit theorem' and its applicability in our case. As I said, our data sample is very special, but I do not have the skills to examine in detail if it has an impact on Carlisle's analyses.

Finally, since the critical report against me by Kranke et al. was published in 2000, I have greatly suffered. Nevertheless, I have continued my clinical and laboratory studies with great care. In addition, there has been confusion concerning the ethical procedures at Ushiku Aiwa General Hospital where I did clinical research. This hospital did not have a formal institutional ethics committee, and therefore I sought and obtained the approval of the Vice-Chairman. Later, while at Toho University School of Medicine, I was unfairly blamed for Ushiku's informal procedures. As a result of a lack of ethical approval, I received the advice of the university authorities and left Toho University.

The only thing I can say is that we performed the tests over years with full honesty and integrity. Additionally, I did not write these articles alone, and some of data were collected by others as well.

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A reply

We thank Dr Fujii for his letter which, unfortunately, does not address the fundamental basis of the analysis of his work [1]. As has been explained [2], the distribution of means sampled from any population of continuous measurements, no matter how bizarre the original distribution of measurements, is always normal/Gaussian (see Fig. 4, reference [2]). Furthermore, the alleles that contribute to individual characteristics behave according to fundamental laws of nature and thus apply to all populations – including the Japanese - however distinct they may be [2, 3].

The statistical principles underlying the analysis [1] are literally universal. Apart from genetics, they apply to the behaviour of tiny particles (e.g. mass-velocity of atoms) and galaxies (e.g. Doppler shifts), and to analyses of the extremes of time (e.g. the speed of light and the slowest radioactive decay). An exception to these mathematical principles would shake the basis of most of modern scientific knowledge and understanding.

Access to Dr Fujii's original data would help us confirm the veracity or otherwise of his claims.

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取手協同病院　臨床研究症例数

藤井氏年間担当症例数

	1990	1991	1992	1993	1994	1995	1997	1998	合計	論文上総症例数	
乳がん	0	6	16	18	11	8	−	−	**59**	**700**	
婦人科(大手術)	13	53	73	57	37	19	−	−	**252**	**1368**	
胆摘	2	5	23	21	22	7	−	−	**80**	**540**	
中耳	0	1	6	2	2	2	−	−	**13**	**500**	
小児斜視	0	1	0	1	2	1	−	−	**5**	**400**	小児斜視･扁摘
小児扁摘	0	6	14	2	4	0	−	−	**26**	**260**	**260**
中絶	0	1	1	0	0	0	−	−	**2**	**80**	
帝王切開	0	1	3	1	1	0	−	−	**6**	**220**	

藤井氏年間全手術担当症例数		397	493	378	340	97	−	−	**1705**	**4328**

施設症例数

	1990	1991	1992	1993	1994	1995	1997	1998	合計
乳がん		20	23	27	23	26	−	−	**119**
婦人科(大手術)		159	119	117	104	90	−	−	**589**
胆摘		2	13	23	27	42	−	−	**107**
中耳		6	8	10	7	10	−	−	**41**
小児斜視		3	2	3	3	4	−	−	**15**
股関節置換術		2	2	2	5	7	−	−	**18**
小児扁摘		23	20	11	16	11	−	−	**81**
中絶		2	0	1	1	0	−	−	**4**
甲状腺		3	3	4	3	8	−	−	**21**
上記症例数　合計		220	190	198	189	198	−	−	**995**

	1990	1991	1992	1993	1994	1995	1997	1998	合計
施設年間麻酔科管理症例数		1028	846	700	688	764	−	−	**4026**

牛久愛和総合病院 臨床研究症例数

藤井氏年間担当症例数

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	合計	論文上総症例数
整形外科	4	1	0	0	0	0	9	5	15	15	27	2	9	23	1	**111**	−
耳鼻科	2	5	0	0	0	0	0	0	0	0	0	0	0	0	0	**7**	−
外科	3	7	0	0	0	0	5	8	5	10	14	2	7	13	0	**74**	−
形成外科	0	0	0	0	0	0	0	0	1	1	3	0	0	1	0	**6**	−
内分泌外科	0	0	0	0	0	0	2	1	4	1	5	0	0	0	0	**13**	−
脳外科	0	1	0	0	0	0	9	2	1	2	6	0	2	2	0	**25**	−
婦人科	1	1	0	0	0	0	9	5	1	2	2	0	0	0	0	**21**	**240**
泌尿器科	0	0	0	0	0	0	2		1	3	1	0	0	0	0	**7**	**−**
口腔外科	0	0	0	0	0	0					1	0	1	2	0	**4**	**−**
甲状腺	0	0	0	0	0	0	2	2	2	0	5	0	0	0	0	**11**	**90**
乳がん	0	0	0	0	0	0	0	0	2	2	5	0	1	2	0	**12**	**100**
胆摘	0	0	0	0	0	0	2	4	2	2	0	0	1	2	0	**13**	**90**
合計	**10**	**15**	**0**	**0**	**0**	**0**	**40**	**27**	**34**	**38**	**69**	**4**	**21**	**45**	**1**	**304**	**990**

筑波大学　臨床研究症例数

藤井氏担当症例数

	1997-2005	論文上総症例数
中耳	15	513
乳癌	86	150
婦人科	24	90
婦人科大手術	346	820
胆摘	44	894
小児扁摘	0	730
甲状腺	89	355
小児斜視	0	120
帝切，腰麻帝切	114	200
歯科抜歯	47	210
膝関節置換	18	80
中絶	99	120
合計	882	4282

筑波大学：麻酔記録、指示・注射処方（術前・当・翌日）、医師記録

術式
甲状腺
調査期間；98～99年

〇：投与
×：非投与

No.	ドロペリドール	メトクラプラミド	デキサメサゾン	オンダンセトロン	グラニセトロン	備考
1	×	×	×	×	×	
2	×	×	×	×	×	
3	×	〇	×	×	×	プリンペランは終刀後に投与（プロトコール違反
4	×	×	×	×	×	
5	×	×	×	×	×	
6	×	×	×	×	×	
7	×	×	×	×	×	
8	×	×	×	×	×	
9	×	×	×	×	×	
10	×	×	×	×	×	
11	×	×	×	×	×	
12	×	×	×	×	×	
13	×	×	×	×	×	
14	×	×	×	×	×	
15	×	×	×	×	×	
16	×	×	×	×	×	
17	×	×	×	×	×	
18	×	×	×	×	×	
19	×	×	×	×	×	
20	×	×	×	×	×	
21	×	×	×	×	×	
22	×	×	×	×	×	
23	×	×	×	×	×	
24	×	×	×	×	×	
25	×	×	×	×	×	
26	×	×	×	×	×	
27	×	×	×	×	×	
28	×	×	×	×	×	
29	×	×	×	×	×	術当日の注射処方なし
30	×	×	×	×	×	
31	×	×	×	×	×	
32	×	×	×	×	×	
33	×	×	×	×	×	
34	×	×	×	×	×	
35	×	×	×	×	×	
36	×	×	×	×	×	
37	×	×	×	×	×	
38	×	×	×	×	×	
39	×	〇	×	×	×	オペ終了時に20 mg投与、プロトコール違反
40	×	×	×	×	×	
41	×	×	×	×	×	
42	×	×	×	×	×	

Manuscript、概要（筑波大学から）　n=
Br J Anaesth 1998: グラニセトロン0, 20, 40, 100 mg, 全身麻酔導入直前　100
Eur J Anaesthesiol 1999: グラニセトロン、ドロペリドール、両方、全身麻酔導入直前　180
その他、取手協同病院から様々

筑波大学：麻酔記録、指示・注射処方（術前・当・翌日）、医師記録

術式
子宮内容除去
調査期間；99～01年

○：投与
×：非投与

No.	ドロペリドール	メトクラプラミド	デキサメサゾン	オンダンセトロン	グラニセトロン	備考
1	×	×	×	×	×	
2	×	×	×	×	×	
3	×	×	×	×	×	
4	×	×	×	×	×	
5	×	×	×	×	×	
6	×	×	×	×	×	
7	×	×	×	×	×	
8	×	×	×	×	×	
9	×	×	×	×	×	
10	×	×	×	×	×	
11	×	×	×	×	×	
12	×	×	×	×	×	
13	×	×	×	×	×	
14	×	×	×	×	×	
15	×	×	×	×	×	
16	×	×	×	×	×	
17	×	×	×	×	×	
18	×	×	×	×	×	
19	×	×	×	×	×	
20	×	×	×	×	×	
21	×	×	×	×	×	
22	×	×	×	×	×	
23	×	×	×	×	×	
24	×	×	×	×	×	
25	×	×	×	×	×	
26	×	×	×	×	×	
27	×	×	×	×	×	
28	×	×	×	×	×	
29	×	×	×	×	×	
30	×	×	×	×	×	
31	×	×	×	×	×	

Manuscript、概要（筑波大学から）　n=
Obstet Gynecol 2002; デキサメサゾン0, 4, 8, 16 mg, 全身麻酔導入直前　120
その他、取手協同病院、東邦大学から

筑波大学：麻酔記録、指示・注射処方（術前・当・翌日）、医師記録

術式	No.	ドロペリドール	メトクラプラミド	デキサメサゾン	オンダンセトロン	グラニセトロン	備考
ラパ胆	1	×	○	×	×	×	オペ終了5時間後に一回投与
調査期間；97～98年	2	×	×	×	×	×	
	3	×	×	×	×	×	

○：投与
×：非投与

Manuscript、概要（筑波大学から）	n=
Eur J Anaesthesiol 1998: グラニセトロン、ドロペリドール、メトクロプラミド、プラセボ、全身麻酔導入	120
Eur J Anaesthesiol 1998: グラニセトロン0, 20, 40, 80 mcg/kg、全身麻酔導入直前	120
Can J Anaesth 1998: グラニセトロン、ドロペリドール、両方、全身麻酔導入直前	150
Can J Anaesth 1999: グラニセトロン or ラモセトロン、手術終了時	80
Eur J Anaesthesiol 2000: グラニセトロンのみ or グラニセトロン+デキサメサゾン、全身麻酔導入直	120
その他、筑波大学から6編	

動物実験(犬)の論文上頭数と研究実施調査結果比較

＜東京医科歯科大学＞　研究記録は現存しないため，研究日から使用頭数を推定し論文数と比較

論文上数	350	＊1991年～1997年
使用犬頭数（推定）	312	＊1989年4月～1995年10月15日，面接結果より週1回研究と仮定

＜筑波大学＞：筑波大学より以下3点の記録を受け取り論文数と比較

・1999年4月～2000年2月犬の搬入出記録
・2002年～2005年　動物実験センター　犬持ち出し記録
・1997年～20006年　動物実験計画書

藤井氏研究

	論文上頭数	犬持ち出し記録
1997	0	50
1998	34	50
1999	120	41
2000	87	50
2001	110	50
2002	117	13
2003	149	9
2004	86	0
2005	24	0
2006	59	－
2007	74	－
2008	24	－
2010	29	－
合計	913	163

高橋氏研究

	論文上頭数	犬持ち出し記録
1997		50
1998		50
1999	10	50
2000	34	50
2001		50
2002		0
2003	18	14
2004		10
2005		0
2006		－
2007		－
2008		－
2010		－
合計	62	274

＊ 1999年　藤井氏犬持ち出し記録は1999年4月～2000年3月31日
＊ 　　：記録現存なし．面接結果より週1回研究として，年間50頭と仮定

probability of propulsion occurring after a postoperative episode of emesis can be predicted by the amount of preoperative exophthalmos. Nonetheless, in patients with significant exophthalmos, a careful history regarding eye problems related to Valsalva or episodes of vomiting may yield eye-opening results and increase the level of suspicion for this rare event that can be associated with PONV.

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Atrioventricular Dissociation

To the Editor:

Cardiac dysrhythmias can be accompanied by significant morbidity and mortality. The following report describes the occurrence of atrioventricular dissociation during the routine induction of general anesthesia.

A 60-yr-old, 75-kg woman with hypertension controlled with verapamil (240 mg) and metoprolol (100 mg) presented for total abdominal hysterectomy. Preoperative electrocardiogram (ECG) revealed sinus rhythm at 62 bpm, and echocardiogram showed left ventricular hypertrophy (LVH). Propofol 140 mg, lidocaine 100 mg, fentanyl 150 μg, and vecuronium 7 mg were delivered IV. The blood pressure decreased from 140/78 to 89/53 mm Hg and the heart rate from 62 to 45 bpm. The ECG showed a bradycardia consistent with atrioventricular dissociation (Figure 1A) that persisted despite ephedrine 10 mg IV and then successive doses of atropine (0.3, 0.8, 1.0, and 2 mg IV). With isoproterenol 4 μg IV, the bradycardia converted to sinus rhythm at 68 bpm (Figure 1B), and the blood pressure increased to 93/51 mm Hg.

Dysrhythmias occur after the administration of several medications. Severe bradycardia and asystole have been attributed to the lack of vagolytic activity of vecuronium in combination with sufentanil or their interaction with the patients' β-adrenergic and/or calcium channel blocker (1). Autonomic imbalance has also been attributed to epidural lidocaine in combination with atenolol and diltiazem (2).

Despite its history of being a hemodynamically neutral muscle relaxant, vecuronium is a possible source of the arrythmia (3). Autonomic imbalance may have been created by the lidocaine and narcotic combination, particularly in the face of β-adrenergic blocker and calcium channel blocker use (2). The existing adrenergic blockade may have caused the ineffectiveness of the indirect-acting sympathomimetic ephedrine. The direct-acting β_1 agoinst isoproterenol may have provided adequate β_1 stimulation to overcome this blockade. Another possible treatment is calcium chloride (4). Because of the LVH, the loss of coordinated atrial contraction may explain the hypotension. Because of the potential for arrhythmias during the administration of anesthetics, diligent ECG monitoring is essential for all patients undergoing anesthesia, especially those taking β and/or calcium channel blockers.

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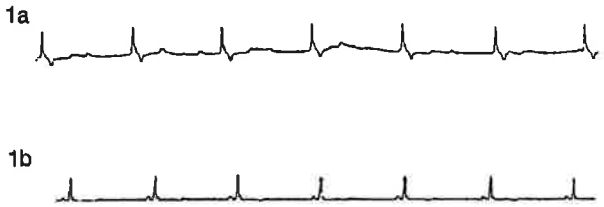

Figure 1. A, After induction, ECG showed atrioventricular dissociation. B, After isoproterenol, ECG returned to sinus rhythm.

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Reported Data on Granisetron and Postoperative Nausea and Vomiting by Fujii et al. Are Incredibly Nice!

To the Editor:

We read with interest the recent article of Fujii et al. (1) about granisetron in the prevention of postoperative nausea and vomiting (PONV). With increasing amazement, we noticed that the results reported by Fujii et al. are incredibly nice and we became skeptical when we realized that side effects were almost always identical in all groups.

During 1994–1999, 47 articles have been published by Fujii et al. (http://www.nlm.nih.gov/> search "Fujii-Y and granisetron") (1–47). In 21 articles, the most frequently reported side effect, headache, is given for the overall 24-h period of observation (Table 1). In 13 articles, the frequency of headache was reported to be identical in all groups (5,7–11,15,16,19,20,29,40,43), while this side effect differed, at most, by one patient per group in the remaining 8 papers (4,6,12–14,27,28,32). Surely, assuming that the study drug has no impact on a side effect, one would expect similar results between the groups. However, identical results are still relatively rare as binominal distribution causes a certain variability in reality. Thus, we tested the null hypothesis that the reported identical incidences could have occurred by chance with the alternative hypothesis that an underlying reason lead to such identical results.

First, the incidence of headache (p) was calculated by the total number of patients with headache (n = 186) divided by the total number of patients (n = 2369) in the 21 studies, resulting in an incidence (with lower to upper 95% confidence intervals) of p = 0.0785 (0.0681 to 0.09).

Second, the probability (P) that x out of n patients will experience headache will generally be calculated according to formula for the binominal distribution $P = (n!/(x!(n - x)!)) \times p^x \times (1 - p)^{n-x}$ (48). Third, for each study, the probability that all (z) groups have identical results with x patients suffering from headache is calculated by $P = P^z$. These calculations were done for x between 0 and 10 as the probabilities for x > 10 were too small to have any impact on the calculation (Table 1).

Fourth, the joint probability that a study results in any identical number of patients is calculated by the sum of the single probabilities for x = 0, 1, 2, . . . 10, also given in Table 1.

Fifth, the joint probabilities of all 18 separate studies with more than two groups–all three studies with two groups had identical results anyway–was in the range of P = 0.0002 to 0.0548. To make it safe and simple, the hypothesis that 10 of 18 studies will result in identical numbers was tested by applying again the above mentioned formula

Table 1. Incidence of Headache per Group in the Investigated Publications and Calculated Probabilities of Obtaining Identical Groups

Reference	Headache/all patients reported groups						Probability that in all groups the identical number of *n* patients will suffer from headache n patients:										Joint probability P
	1	2	3	4	5	6	0	1	2	3	4	5	6	7	8	9	10	
Acta Anaesthesiol Scand 1997;41:746–749	2/25	2/25					1.68E-02	7.61E-02	7.95E-02	3.39E-02	7.45E-03	9.53E-04	7.69E-05	4.11E-06	1.51E-07	3.91E-09	7.26E-11	0.2148
Acta Anaesthesiol Scand 1997;41:1167–1170	2/30	2/30	2/30	2/30			5.49E-05	2.34E-03	5.45E-03	2.18E-03	2.38E-04	9.17E-06	1.46E-07	1.06E-09	3.81E-12	7.16E-15	7.34E-18	0.0103
Acta Anaesthesiol Scand 1998;42:220–224	2/30	2/30	2/30	2/30			5.49E-05	2.34E-03	5.45E-03	2.18E-03	2.38E-04	9.17E-06	1.46E-07	1.06E-09	3.81E-12	7.16E-15	7.34E-18	0.0103
Acta Anaesthesiol Scand 1998;42:653–657	2/30	2/30	2/30	2/30			5.49E-05	2.34E-03	5.45E-03	2.18E-03	2.38E-04	9.17E-06	1.46E-07	1.06E-09	3.81E-12	7.16E-15	7.34E-18	0.0103
Anesth Analg 1997;85: 913–917	3/45	3/45	3/45	3/45	3/45	3/45	2.59E-10	8.23E-07	3.56E-05	1.18E-04	6.05E-05	7.03E-06	2.36E-07	2.70E-09	1.18E-11	2.18E-14	1.82E-17	0.0002
Br J Anaesth 1998;81: 387–389	4/50	4/50	4/50				4.72E-06	3.65E-04	3.32E-03	8.40E-03	8.43E-03	4.06E-03	1.06E-03	1.62E-04	1.56E-05	9.80E-07	4.17E-08	0.0258
Br J Anaesth 1998;81: 390–392	2/40	2/40	2/40	2/40			2.09E-06	2.81E-04	2.14E-03	2.90E-03	1.12E-03	1.58E-04	9.66E-06	2.83E-07	4.32E-09	3.63E-11	1.77E-13	0.0066
Can J Anaesth 1995;42: 387–390	1/22	1/22	1/22	1/22			7.51E-04	9.26E-03	5.93E-03	6.17E-04	1.65E-05	1.46E-07	4.96E-10	7.14E-13	4.64E-16	1.43E-19	2.15E-23	0.0166
Can J Anaesth 1995;42: 852–856	1/25	2/25	1/25	1/25			2.82E-04	5.79E-03	6.32E-03	1.15E-03	5.54E-05	9.09E-07	5.91E-09	1.69E-11	2.28E-14	1.53E-17	5.27E-21	0.0136
Can J Anaesth 1996;43: 35–38	2/25	2/25					1.68E-02	7.61E-02	7.95E-02	3.39E-02	7.45E-03	9.53E-04	7.69E-05	4.11E-06	1.51E-07	3.91E-09	7.26E-11	0.2148
Can J Anaesth 1996;43: 110–114	2/25	2/25	2/30	2/30			2.82E-04	5.79E-03	6.32E-03	1.15E-03	5.54E-05	9.09E-07	5.91E-09	1.69E-11	2.28E-14	1.53E-17	5.27E-21	0.0136
Can J Anaesth 1996;43: 660–664	2/20	2/20	2/20	2/20			1.44E-03	1.22E-02	5.22E-03	3.56E-04	6.12E-06	3.38E-08	6.95E-11	5.86E-14	2.15E-17	3.58E-21	2.76E-25	0.0192
Can J Anaesth 1996;43: 1095–1099	2/24	2/23	2/23				2.78E-03	2.37E-02	2.23E-02	5.44E-03	4.87E-04	1.93E-05	3.78E-07	3.97E-09	2.36E-11	8.19E-14	1.71E-16	0.0548
Can J Anaesth 1996;43: 1229–1232	2/30	2/30					7.41E-03	4.84E-02	7.38E-02	4.67E-02	1.54E-02	3.03E-03	3.81E-04	3.25E-05	1.95E-06	8.46E-08	2.71E-09	0.1952
Can J Anaesth 1997;44: 273–277	2/20	2/20	2/26	2/25			1.44E-03	1.22E-02	5.22E-03	3.56E-04	6.12E-06	3.38E-08	6.95E-11	5.86E-14	2.15E-17	3.58E-21	2.76E-25	0.0192
Can J Anaesth 1997;44: 489–493	2/25	2/25	3/35	3/35			2.82E-04	5.79E-03	6.32E-03	1.15E-03	5.54E-05	9.09E-07	5.91E-09	1.69E-11	2.28E-14	1.53E-17	5.27E-21	0.0136
Can J Anaesth 1997;44: 820–824	3/30	3/30	2/30	3/30			5.49E-05	2.34E-03	5.45E-03	2.18E-03	2.38E-04	9.17E-06	1.46E-07	1.06E-09	3.81E-12	7.16E-15	7.34E-18	0.0103
Can J Anaesth 1998;45: 153–156	3/30	2/30	2/30				6.38E-04	1.06E-02	2.01E-02	1.01E-02	1.92E-03	1.67E-04	7.45E-06	1.86E-07	2.73E-09	2.46E-11	1.41E-13	0.0435
Can J Anaesth 1998;45: 541–544	4/50	3/50	4/50				4.72E-06	3.65E-04	3.32E-03	8.40E-03	8.43E-03	4.06E-03	1.06E-03	1.62E-04	1.56E-05	9.80E-07	4.17E-08	0.0258
Eur J Anaesthesiol 1999; 16:62–65	3/30	3/30	3/30	3/30			5.49E-05	2.34E-03	5.45E-03	2.18E-03	2.38E-04	9.17E-06	1.46E-07	1.06E-09	3.81E-12	7.16E-15	7.34E-18	0.0103
Eur J Anaesthesiol 1999; 16:376–379	4/50	4/50	4/50				4.72E-06	3.65E-04	3.32E-03	8.40E-03	8.43E-03	4.06E-03	1.06E-03	1.62E-04	1.56E-05	9.80E-07	4.17E-08	0.0258

【資料 10 - 3】

for the binominal distribution with the highest probability of 0.0548. This resulted in a final probability (P_{final}) that 10 of those 18 studies will have identical results by chance of $P_{final} = 6.78 \times 10^{-9}$!

Thus, we have to reject the null hypothesis that the frequency of identical results simply occurred because of the assumption that the incidence of headache is not affected by the intervention, and we have to conclude that there must be an underlying influence causing such incredibly nice data reported by Fujii et al.

We thank Horst Fassl, Emeritus Professor of Medical Statistics (Nieder-Olm, Germany) and Herbert Vogt, Professor of Mathematics (Dept. of Applied Mathematics, University of Wuerzburg, Germany) for their statistical advice.

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In Response:

Thank you for the opportunity to answer the questions by a reader of *Anesthesia & Analgesia*. As previously described in the first report by us (1), we evaluated the efficacy and safety of granisetron, a selective 5-hydroxytryptamine Type 3 ($5\text{-}HT_3$) receptor antagonist, for preventing postoperative nausea and vomiting (PONV) in women undergoing major gynecologic surgery. Consequently, granisetron was effective for the control of PONV after major gynecologic surgery, with little adverse event. Since then, we have investigated to assess the prophylactic antiemetic therapy with granisetron for preventing PONV after various types of surgery, such as pediatric tonsillectomy, breast surgery, middle ear surgery, and thyroidectomy, with a relatively high incidence of PONV when no prophylactic antiemetic is given.

Granisetron lacks the sedative, dyspholic, and extrapyramidal symptoms associated with non-$5\text{-}HT_3$ receptor antagonist (e.g., droperidol, metoclopramide) (2,3). Mild headache occurs in patients receiving granisetron for preventing chemotherapy-induced emesis (4). Similarly, in a number of our studies regarding granisetron and PONV, we found that several patients who had received granisetron experienced mild headache and that an incidence of headache was approximately 10%. Consequently, an incidence of headache seems to be identical, but it was true. How much evidence is required to provide adequate proof about

【資料 10 - 4】

antiemetics' adverse events introduced recently by several investigators?

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Nonpharmacologic Sedation in a Deaf Child

To the Editor:

A 3-yr-old child was referred to our institution for a magnetic resonance imaging (MRI) examination of the ears. He had a partial deafness. Previously, he underwent an unilateral cochlear implant, which had failed. The MRI examination was performed to find the cause of the failure.

When asked about fasting hours, his father admitted that the child had eaten 30 min before the time set for the examination. Because of a very busy schedule, it was not possible to postpone his examination. It was decided after consulting with his father to try to put him to sleep "naturally." His father took him in his arms and, indeed, he fell asleep. We were able to proceed with the MRI scan for 45 min uneventfully. It was a good alternative because in this particular case, we did not need to inject gadolinium contrast (so no need for an IV line). In addition, because of his deafness, the noise of the MRI machine did not wake the child, and he remained motionless.

For ambulatory pediatric sedation, a natural sleep is, in certain conditions, an alternative that should be kept in mind.

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Fiberoptic Endotracheal Intubation Through an Ultra-Thin Bronchoscope with Suction Channel in a Newborn with Difficult Airway

To the Editor:

Management of the airway may be difficult in newborns with craniofacial and neck malformations (1). Previous experiences with flexible endoscopic intubation in neonates have shown encouraging results, but a number of limitations, such as no directional control at the tip or lack of an operative channel, were also reported (2,3). We describe a successful intubation by a new 2.5-mm fiberoptic bronchoscope with a 1.2-mm suction channel in a newborn with difficult airway.

A 2300-g infant, born at 35 wk of gestation after an urgent cesarean delivery for fetal distress, needed cardiopulmonary resuscitation at birth. Endotracheal intubation was achieved only after several attempts with a 3.0-mm tube inserted nasotracheally. On arrival to our unit, physical examination showed dysmorphic face, micrognathia, and arthrogryposis. A gross air leak around the endotracheal tube (ETT) prevented an adequate ventilation of the patient. We decided to explore the patient's larynx before exchanging the ETT with a larger one, but micrognathia did not allow proper visualization by conventional laryngoscopy. Thus, we inserted a 3.5-mm ETT using a fiberoptic flexible bronchoscope (Richard Wolf-GmbH, Knittlingen, Germany). This endoscope has a 2.5-mm outer diameter, a 1.2-mm instrument channel, an angle of deflection at the tip of 160° up and 130° down, and a working length of 450 mm (Figure 1). During the procedure, we could remove secretions and provide topical anesthesia via the suction channel of the endoscope. No complications were noted.

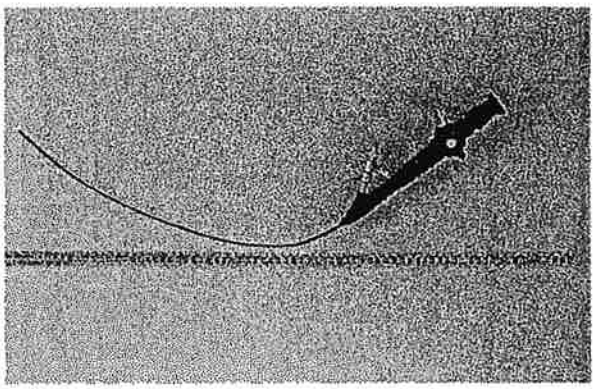

Figure 1. Fiberoptic flexible bronchoscope.

We believe this new ultra-thin bronchoscope may be useful in newborns and small infants when a difficult intubation is anticipated or, alternatively, when lower airway evaluation, suctioning, bronchoalveolar lavage, or supplemental oxygen delivery during intubation is required.

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Which Intravenous Sodium Channel Blocker for Neuropathic Pain?

To the Editor:

McCleane's (1) comparison of IV phenytoin with placebo to relieve neuropathic pain is of interest in an area in which the only two previously controlled trials with oral phenytoin produced conflicting results (2,3).

However, McCleane's study statistically analyzes mean pain scores rather than determining from individual patient scores clinical significance, i.e., >50% pain relief and >75% relief. The decrease in overall pain score (0–10 linear visual analog score) in the phenytoin group from a mean (±SD) of 4.62 (±3.46) to 3.25 (±2.95) does not quantify the "significant benefit" judged by 8 of 20 patients, making comparison with other analgesics difficult. Furthermore, although both groups included the same patients, the mean overall pain score in the placebo group preinfusion was much higher 7.18 (±1.47) than the phenytoin group 4.62 (±3.46), suggesting a significant change in pain severity during the week between infusions, which would affect outcome.