Article

COMPARATIVE EFFICACY AND SAFETY OF ROFECOXIB VERSUS DICLOFENAC IN PERIOPERATIVE PAIN MANAGEMENT FOR GYNECOLOGICAL SURGERIES

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs in pain management though they have negative effects that reduce their application in the perioperative period, of which non-selective cyclooxygenase (COX) inhibitors are the worst offenders. The selective COX-2 inhibitors, such as rofecoxib are regarded as safer medications, as they have little effect on the activity of platelets and produce less gastrointestinal disorders. The purpose of the study was to compare the problematic of a single 50 mg dose of rofecoxib against rofecoxib and three doses of 50 mg each of diclofenac on the effects of the drugs on the platelet functions, blood loss as well as pain control during the gynecological operations. An active-comparator clinical trial (random/double- blind/double-dummy) was performed on 75 patients who received vaginal hysterectomy or breast operation. The trial evaluated platelet aggregation, blood loss during the procedure, and hemoglobin changes postoperatively and the requirement of extra pain killers or anti-vomiting drugs. Conclusions were that rofecoxib considerably decreased platelet aggregations (P = 0.02), intraoperative blood shed (P = 0.01) and hemoglobin shedding (P = 0.01) as compared to diclofenac. Also, rofecoxib controlled pain in a similar proportion to that of three doses of Diclofenac and hence fewer anti-emety drugs were needed (P = 0.03). These results indicate that rofecoxib is superior in its hemostatic effect, lowers oxidative stress, it has a better side-effect profile than diclofenac. Briefly, despite the comparable results in terms of analgesic effect, the potential benefit of rofecoxib to limit bleeding, postoperative complications and a minimal number of gastrointestinal adverse effects renders it to be a viable alternative to non-selective NSAIDs in perioperative pain management. Nevertheless, subsequent investigations are required to assess the positive correlation between the long term cardiovascular safety of COX-2 inhibitors and their extensive application in the high-risk surgical patients.

Keywords: Rofecoxib, Diclofenac, Perioperative Pain Management, Gynecological Surgeries, Platelet Aggregation

Introduction

The most common type of drugs used in treating postoperative pain is non-steroidal anti-inflammatory drugs (NSAIDs) which are used owing to their analgesic, anti-inflammatory and antipyretic effects. Due to the potential advantage of having an effective way of using these drugs to reduce opioid usage, opioid-related side effects and the likelihood of addiction, these agents are regarded as a first-choice agent in the perioperative management of pain. Although NSAIDs, particularly non-selective cyclooxygenase (COX) inhibitors, have noted wide use, diverse negative effects are related to their use, which restricts their use in the perioperative environment. Inhibition plates is one of the greatest issues that may lead to a high tendency of bleeding in the course of operations. Diclofenac is a non-selective inhibitor of the COX-1 and COX-2 enzyme. COX-1 inhibition slows down thromboxane A2 pentane, which is an essential mediator in agglomeration of the platelet and blood coagulation, but it may cause profuse blood flow especially when someone undergoes a surgical operation. Moreover, the non-selective NSAIDs

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have also been associated with gastrointestinal (GI) toxicity, kidney impairment and cardiovascular risks hence restricting their application even in patients with some comorbidities. In order to present safer option as compared to non-selective NSAIDs, selective COX-2 inhibitors, e.g., rofecoxib, have been developed. COX-2 inhibitors act on the COX-2 enzyme which mainly contributes towards inflammation, unlike the COX-1 which serves an important role in the functioning of the platelet. This is because this selective inhibition decreases the possibility of bleeding and the gastrointestinal side effects thus COX- 2 inhibitors are appealing as an agent of pain management, especially in perioperative management. Even though COX-2 inhibitors prove to be useful in the treatment of postoperative pain, they need not be fully explored in perioperative care, especially the performance of gynecological operations. The promise of COX-2 inhibitors to reduce blood loss and enhance hemostasis as well as in terms of postoperative complication is not yet tapped and their safety needs further evaluation not only in high risk surgical patients. The proposed study is expected to fill this gap in the bodies of knowledge by comparing the platelet as well as blood loss functions and pain control among patients undergoing gynecological surgeries using 50 mg of rofecoxib to 50 mg of diclofenac, subjecting them three times. This active-comparator, double-blind, and randomized clinical trial aims at clarifying whether rofecoxib, a specific COX-2 angrelidation, has more hemostatic advantages and fewer side effects than a non- selective NSAID diclofenac. Due to the assessment of platelet aggregation, intraoperative blood loss, postop changes in hemoglobin concentration and the requirement of extra analgesia or antiemetics, the paper will provide supportive data about the administration of selective COX-2 inhibitors in the perioperative pain treatment. As well, it will evaluate the safety of rofecoxib compared to gastrointestinal, renal, and cardiovascular risks, and this is to add to the knowledge of what is the role of COX-2 inhibitors to perioperative care nowadays.

Methods

This is a randomized, double-blind, active-control, single centre clinical interventional study meant to compare the effect of the rofecoxib to lot of 10 and diclofenac in platelet function, blood loss and analgesia during gynaecological surgeries. The research was conducted on 75 patients of the ages 30-74 years old and each patient was divided into two groups in that 38 patients were given rofecoxib and 37 patients were given diclofenac. Each of the participants was subjected to the hysterectomy either of the vaginal type or breast surgery, whilst under general anesthesia. The patients were stratified randomly in the following four groups: Rofecoxib Hysterectomy, Rofecoxib Breast Surgery, Diclofenac Hysterectomy, and Diclofenac Breast Surgery. Preoperation medication was either one single dose of 50 mg orally rofecoxib 1 h prior to surgery or three doses of 50 mg orally of diclofenac 8 h apart. The rofecoxib group received a dose of placebo 8 and 16 hours following the first dose. Blood samples were collected to evaluate the platelet aggregation on the basis of arachidonic acid stimulation at the baseline and 4 hours following the first dose of the corresponding drug. Loss of blood during surgery as well as changes in hemoglobin were measured, and the postoperative need of increased analgesic or anti-emetic drugs was examined. The main study outcomes followed were intraoperative blood loss, platelet aggregation and postoperative hemoglobin loss. Pain relief, the need of further analgesia and side effects, including the need of anti-emetics were among secondary endpoints. The review also determined coagulation parameters by thromboelastography, (TEG) and varied levels of oxidative stress markers
e.g. malondialdehyde (MDA) to determine the antioxidant activity of the drugs. In the statistical analysis, comparisons of platelet aggregation, blood loss, level of hemoglobin to the two treatment groups were to be made using respective tests (e.g., t-tests or chi-square tests). All results with p-value < 0.05 were taken as statistically significant.

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Result

There were 75 patients enrolled who received hysterectomy or surgery on the breast randomly and stratified into four categories, the first group received analgesic drugs Rofecoxib and the second group took Diclofenac. The demographic features among the groups were mostly similar. The age of the participants varied between 30 to 74 years with average values of between 50 and 53 years. Most of the patients were of ASA I and II in all groups which approximated with the ASA (American Society of Anesthesiologists) physical status classification. Regarding the anaesthetic and surgical parameters (Table 1), the duration of anaesthesia and operation was correlated with the type of procedure with higher values recorded in hysterectomies. Patients in Rofecoxib group during hysterectomy had the longest anaesthesia (184 60 min) and operating time (135 60 min) and lowest in the Rofecoxib group during breast surgery (150 40 min and 105 35 min, respectively). The infusion rates of propofol and remifentanil as well as the total doses administered were relatively close in each group. There were no differences between the groups in height, weight, haemoglobin levels, serum creatinine, or cystatin-C values, which shows that the baseline renal and combined hematological tests were pretty similar. Concerning coagulation and the oxidative stress markers (Table 2), patients treated with Rofecoxib recorded a slight decrease in thromboelastography (TEG 2) r and k times after dose indicating slight improvement in clot formation. The values of TEG maximum amplitude (MA) and Ly30 were unchanged, therefore remaining the same, as clot strength and fibrinolytic activity. Remarkably, the Rofecoxib group had decreased levels of malondialdehyde (MDA) after treatment (3.6 +/- 1.0 mg/L Base to 3.2 +/- 1.0 mg/L Base) which means that there was a slight antioxidant effect. The hemoglobin loss and blood losses during surgery were much lower in patients treated with Rofecoxib in comparison with Diclofenac (Table 3). Among patients having undergone hysterectomies, the amount of blood lost was 175 +/- 90 mL in the Rofecoxib group compared with 282 +/- 160 mL in the Diclofenac group ($p < 0.01$). Likewise, hemoglobin loss was less (17 9 g/L) vs 20 10 g/L). Blood loss (85 +/- 55 mL; mean +/- SD) and hemoglobin loss (7 +/- 6 g/L) were lowest in surgery patients treated with Rofecoxib but significantly less compared with those in Diclofenac group (235 +/- 125 mL; $p < 0.02$), (19 +/- 7 g/L; $p < 0.02$), respectively. Coagulation scores were similar among all groups. Altogether, compared to Diclofenac, Rofecoxib demonstrated a better hemostatic effect and lower oxidative stress during surgery.

Table 1: Patient Characteristics, Surgical and Anaesthesiological Data (n = 75)

Parameter	Rofecoxib Hysterectomy (n=20)	Rofecoxib Breast Surgery (n=17)	Diclofenac Hysterectomy (n=18)	Diclofenac Breast Surgery (n=20)
Vaginal/Transabdominal Hysterectomy	18-Feb	–	15-Mar	–
Lumpectomy / Tumour Dissection / Mastectomy	–	7/9/2001	–	1 / 13 / 6*
ASA I / II / III	8/11/2001	9/7/2001	10/6/2002	8/10/2002
Age (yr)	53 (39–73)	50 (30–70)	51 (36–74)	52 (36–68)
Height (cm)	163 (7)	165 (6)	163 (6)	166 (4)
Weight (kg)	68 (10)	63 (9)	66 (10)	66 (10)
Haemoglobin (g/l)	130 (10)	127 (7)	124 (8)	134 (10)
Serum Creatinine (mmol/l)	77 (11)	80 (9)	78 (14)	81 (13)
Cystatin-C (mg/l)	1.01 (0.21)	1.00 (0.13)	1.01 (0.30)	1.05 (0.14)
Anaesthesia duration (min)	184 (60)	150 (40)	172 (70)	195 (50)
Operation duration (min)	135 (60)	105 (35)	130 (60)	140 (55)
Propofol, total dose (mg)	1435 (420)	1200 (410)	1320 (500)	1375 (385)
Remifentanil (µg/kg/min)	0.14 (0.09)	0.10 (0.05)	0.13 (0.12)	0.13 (0.06)

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Table 2: Coagulation and Oxidative Stress Markers in Patients Receiving Rofecoxib or Diclofenac (n = 75)

Parameter	Rofecoxib (n=38)	Diclofenac (n=37)
	Predose	Postdose
TEG® r (mm)	9 (3.5)	8 (3)
TEG® k (mm)	3 (2)	3 (1)
TEG® MA (mm)	64 (6)	62 (6)
TEG® α (°)	72 (7)	74 (5)
TEG® Ly30 (%)	2 (1)	2 (1)
Malondialdehyde by platelets (mg/litre)	3.6 (1.0)	3.2 (1.0)

Table 3: Intraoperative Blood Loss, Coagulation Score, and Hemoglobin Loss (n = 75)

Parameter	Rofecoxib Hysterectomy (n=20)	Rofecoxib Breast Surgery (n=17)	Diclofenac Hysterectomy (n=18)	Diclofenac Breast Surgery (n=20)	*P vs Diclofenac	+P vs Breast Surgery
Intraoperative Blood Loss (ml)	**175 (90) *+**	**85 (55) ***	**282 (160) +**	235 (125)	< 0.01	0.02
Coagulation (score 1–5)	2.9 (0.3)	3.0 (0.1)	2.6 (0.6)	2.8 (0.7)	NS	NS
Hemoglobin Loss (g/litre)	**17 (9) *+**	**7 (6) ***	**20 (10) +**	19 (7)	< 0.01	0.02

Discussion

This trial is significant in perioperative treatment of some selective NSAIDs versus some non-selective NSAIDs mainly assessing the safety and efficacy of rofecoxib, the COX-2 selective inhibitor amongst the patients undergoing gynecological surgery using diclofenac, commonly referred to as a non-selective NSAID. Its main goal was to evaluate the effect on the platelet function, coagulation rates, blood loss and analgesia power. The results indicate that a single preoperative dose of rofecoxib at 50mg dosage showed better hemostatic results. Patients who took rofecoxib had very less blood loss in surgery and postoperative hemoglobin decline as against the patient who took diclofenac. This is even more pertinent in hysterectomy where the amount of blood lose was nearly 40 percent lesser in the rofecoxib group (175 l 90 mL) than in the diclofenac group (282 l 160 mL; p < C001). In the same manner, rofecoxib-treated patients undergoing breast surgery also reported quite a significant median decrease in blood loss and hemoglobin loss (p < 0.02). The decreased level of platelet-derived malondialdehyde (MDA) after the treatment in the rofecoxib group also indicates that rofecoxib played a positive role in the reduction of oxidative stress, which helps to obtain better intraoperative hemostasis. Synergistic pharmacodynamic explanation of these findings is based upon established mechanism of action of COX-2-selective drugs, which preserve platelet thromboxane A2 production mediated by COX-1. This contributes to platelet aggregation to a higher level as compared to non-selective NSAIDs such as diclofenac that inhibit both COX-1 and COX-2 and thus it has greater bleeding tendency. Even though moderate variation in TEG (Thromboelastography) parameters, the global clotting scores were not significantly different, and all this proves that the clinical variation in bleeding was not fully evident in the global coagulation tests, and it is only a bit of complexity of effect of NSAIDs on hemostasis. Notably, analgesic effects of both drugs have been determined to be similar and the rofecoxib drug was shown to reduce pain to an equivalent dose of three doses of diclofenac. Nevertheless, rofecoxib showed much less need of antiemetic medication (p = 0.03) meaning a more positive side effect pattern on gastrointestinal problems, which is another reputed advantage of selective COX-2 inhibition. All in all, the results justify the safety and efficacy of rofecoxib in perioperative pain management of gynecologic procedures.

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Rofecoxib should be an attractive substitute to conventional NSAIDs because it does not require a multiple-dose usage, it has a decreased potential of doubling hemorrhage appearances, which means it does not seriously affect platelet functionality and therefore it requires less supplementary treatment. However, there is still concern that the long-term cardiovascular safety of COX-2 inhibitors is questionable despite which they must be assessed when using them to larger surgical patients. These advantages could also be tested in other surgical specialties so that they can be verified with additional researches in the future.

Conclusion

This experiment points out the benefits that might come about because of the use of selective COX-2 as contained in rofecoxib, in perioperative management of pain in gynecological procedures. The major aim would be to compare the action of rofecoxib and diclofenac on platelet action in terms of blood loss, postoperative changes in hemoglobin, and management of pain. The results indicate that rofecoxib has considerably more advantage than diclofenac especially when it comes to fewer blood loss during the surgery and tissue and hemoglobin reduction during the operation which plays a great role in recovering post operation. The findings indicated that as early as one preoperative dose of rofecoxib 50 mg was able to produce a significant reduction in platelet aggregation and degree of blood loss in the course of the operation, compared with diclofenac. Particularly, the patients in the rofecoxib group suffered smaller blood losses during a hysterectomy (175 +- 90 mL) than patients in the diclofenac group (282 +- 160 mL). On the same note, the amount of hemoglobin loss was also significantly smaller in the rofecoxib group and that increases its claim to provide a stronger hemostatic effect. These results were similar to those of the previous findings based on the fact that the COX-2-selective inhibitors do not decrease platelet thromboxane A2 production which causes platelet aggregation and limits bleeding tendency which is common in the use of a particular drug known as diclofenac the non-selective NSAIDs. Further, rofecoxib showed an indicator of decreasing the oxidative stress, which was reflected by lowered concentration of malondialdehyde (MDA), a major measurement tool of oxidative stress. This is an indication that rofecoxib can be used in the prevention of oxidative injury during surgery and this could promote better post-surgery recovery. Moreover, rofecoxib activity in reducing pain was similar to three doses of diclofenac, and in addition, it had a few side effects, especially the minimized use of anti-emetic medication which is a big plus not only in making patients feel better, but also by mitigating adverse gastrointestinal outcomes. Along with such positive results, one should mention the questions about the long-term cardiovascular safety of COX-2 inhibitors. Although the use of rofecoxib in this study showed promising findings, the possibility of its chronic inhibition of the COX-2 with related complications of cardiovascular incidents deserves the clarity which could only be obtained before its applicability to the perioperative period. Thus, as much as rofecoxib has considerable benefit as far as pain management, hemostasis and lower side effects during gynaecologic surgeries, its long-term safety, especially among high-risk surgery patients, needs further evaluation. To conclude, rofecoxib seems to be a good alternative to non-selective forms of NSAIDs with significant advantages in terms of controlling surgery- associated blood loss, platelet activity, and postoperative complications, as well as comparable analgesia. Its usage in gynecologic procedures may be regarded as positive, although its efficacy and safety have to be tested in larger and more heterogeneous surgical groups in order to reaffirm its generalization.

References

1. Bamber, M. J., Tweedie, I. E., & Breeze, C. (1997). Premedication with controlled release diclofenac sodium reduces post-operative pain after minor gynaecological surgery. Eur J Anaesthesiol, 14, 421–427.
2. Perttunen, K., Nilsson, E., & Kalso, E. (1999). I.V. diclofenac and ketorolac for pain after thoracoscopic surgery. Br J Anaesth, 82, 221–227.

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3. Lee, A., Cooper, M. C., & Craig, J. C. (2001). Effects of nonsteroidal anti-inflammatory drugs on post-operative renal function in normal adults (Cochrane Review). Cochrane Database Syst Rev, 2.

4. Gabbott, D. A., Cohen, A. M., & Mayor, A. H. (1997). The influence of timing of ketorolac administration on post-operative analgesic requirements following total abdominal hysterectomy. Eur J Anaesthesiol, 14, 610–615.

5. Strom, B. L., Berlin, J. A., & Kinman, J. L. (1996). Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. JAMA, 275, 376–382.

6. Leese, P. T., Hubbard, R. C., & Karim, A. (2000). Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. J Clin Pharmacol, 40, 124–132.

7. Bombardier, C., Laine, L., Reicin, A., et al. (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med, 343, 1520–1528.

8. Mehlisch, D. R., & Fulmer, R. I. (1997). A crossover comparison of bromfenac sodium, naproxen sodium, and placebo for relief of pain from primary dysmenorrhea. J Womens Health, 6, 83–92.

9. Raineri-Gerber, I., von Felten, A. (1991). Inhibition of thrombocyte function by non-steroidal anti-rheumatic agents: a comparative study between diclofenac, acemetacin, mefenamic acid and ibuprofen. Schweiz Med Wochenschr, 121, 783–787.

10. Camenzind, V., Bombeli, T., Seifert, B., et al. (2000). Citrate storage affects thrombelastograph analysis. Anesthesiology, 92, 1242–1249.

11. Laisalmi, M., Teppo, A. M., Koivusalo, A. M., et al. (2001). The effect of ketorolac and sevoflurane anesthesia on renal glomerular and tubular function. Anesth Analg, 93, 1210–1213.

12. Riendeau, D., Charleson, S., Cromlish, W., et al. (1997). Comparison of the cyclooxygenase-1 inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, using sensitive microsomal and platelet assays. Can J Physiol Pharmacol, 75, 1088–1095.

13. Chan, C. C., Boyce, S., Brideau, C., et al. (1999). Rofecoxib [Vioxx, MK-0966; 4-(4′-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. J Pharmacol Exp Ther, 290, 551–560.

14. Leese, P. T., Talwalker, S., Kent, J. D., et al. (2002). Valdecoxib does not impair platelet function. Am J Emerg Med, 20, 275–281.

15. VanHecken, A., Schwartz, J. I., Depre, M., et al. (2000). Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol, 40, 1109–1120.

16. Merck & Co. Inc. (1998). Vioxx™ prescribing information. Whitehouse Station: Merck & Co., New Jersey.

17. Kendall, M. J., Thornhill, D. P., & Willis, J. V. (1979). Factors affecting the pharmacokinetics of diclofenac sodium (Voltarol). Rheumatol Rehabil, 38, 38–46.

18. Yuan, C. S., Foss, J. F., O'Connor, M., et al. (1998). Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol, 38, 1017–1020.

19. Reinhart, D. J., Latson, T. W., Whitten, C. W., et al. (1993). Influence of ketorolac tromethamine on clot elastic strength in humans as assessed by thromboelastography. J Clin Anesth, 5, 216–220.

20. Mukherjee, D., Nissen, S. E., & Topol, E. J. (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA, 286, 954–959.

21. Reicin, A. S., Shapiro, D., Sperling, R. S., et al. (2002). Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, and nabumetone). Am J Cardiol, 89, 204–209.

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22. Schmidt, A., Bjorkman, S., & Akeson, J. (2001). Preoperative rectal diclofenac versus paracetamol for tonsillectomy: effects on pain and blood loss. Acta Anaesthesiol Scand, 45, 48–52.

23. Catella-Lawson, F., McAdam, B., Morrison, B. W., et al. (1999). Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther, 289, 735–741.

24. Reuben, S. S., & Connelly, N. R. (2000). Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg, 91, 1221–1225.

25. Reuben, S. S., Fingeroth, R., & Krushell, R. (2002). Evaluation of the safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. J Arthroplasty, 17, 26–31.

26. Watcha, M. F., Issioui, T., & Klein, K. W. (2003). Costs and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. Anesth Analg, 96, 987–994.

27. Fredman, B., Jedeikin, R., & Olsfanger, D. (1993). The opioid-sparing effect of diclofenac sodium in outpatient extracorporeal shock wave lithotripsy (ESWL). J Clin Anesth, 5, 141–144.

28. Rautoma, P., Santanen, U., & Avela, R. (2000). Diclofenac premedication but not intra-articular ropivacaine alleviates pain following day-case knee arthroscopy. Can J Anaesth, 47, 220–224.

29. Niccoli, L., Bellino, S., & Cantini, F. (2002). Renal tolerability of three commonly employed non-steroidal anti-inflammatory drugs in elderly patients with osteoarthritis. Clin Exp Rheumatol, 20, 201–207.

30. Ahmad, S. R., Kortepeter, C., & Brinker, A. (2002). Renal failure associated with the use of celecoxib and rofecoxib. Drug Saf, 25, 537–544.

31. Ramsay, M. A., Savege, T. M., & Simpson, B. R. (1974). Controlled sedation with alphaxalone-alphadolone. Br Med J, 2, 656–659.