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Extended Research Article

Gabapentin as an adjunct to multimodal pain regimens in surgical patients: the GAP placebo-controlled RCT and economic evaluation

Sarah Baos,[1] Terrie Walker-Smith,[1] Mandy Lui,[1] Elizabeth A Stokes,[2] Jingjing Jiang,[2] Maria Pufulete,[3] Ben Gibbison[3,4*] and Chris A Rogers[1] and on behalf of The GAP Investigators

[1]Bristol Trials Centre, Bristol Medical School, University of Bristol, Bristol, UK
[2]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]Bristol Heart Institute, Bristol Medical School, University of Bristol, Bristol, UK
[4]Bristol Royal Infirmary, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

[*]**Corresponding author** ben.gibbison@bristol.ac.uk

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Scientific summary

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Scientific summary

Background

There are around 4.9 million episodes of surgery per year in the UK – 1.5 million of these are classified as *major* surgery, procedures which cost the NHS upwards of £5.5B per year. Up to 40% of patients report severe pain after surgery that negatively impacts their recovery. Optimal postoperative pain management not only meets the humanitarian imperative to alleviate suffering, but also provides benefits in terms of reduced length of hospital stay and reduced chronic postsurgical pain. These have consequent positive impacts on quality of life and well-being.

Gabapentin is a medicine frequently added to multimodal analgesic regimens after surgery to try and reduce the use of opioid drugs (which can cause somnolence, dizziness and respiratory depression) while controlling pain effectively. It is an anticonvulsant medication with a UK licence to treat partial seizures and neuropathic pain. It is also used off-licence for acute pain. It reduces voltage-gated calcium channel activity in the central neurones and therefore reduces neuronal firing and neurotransmitter release.

There are over 130 randomised controlled trials (RCTs) that have investigated gabapentin versus placebo in different surgical populations. Most are small (< 200 patients, median 80) and highly heterogeneous, both statistically and clinically. Because of the absence of evidence for both the benefits and harms of gabapentin in the perioperative setting, the UK National Institute for Health and Care Excellence issued a 'recommendation for research' in the most recent guidance for perioperative care.

Objectives

The GAP study aimed to test the hypothesis that gabapentin reduces opioid use after major surgery and speeds up recovery, thereby reducing postoperative hospital stay compared to standard multimodal analgesia.

Methods

Study design

A multicentre, parallel-group, placebo-controlled, pragmatic RCT comparing the effectiveness, cost-effectiveness and safety of gabapentin as an adjunct to standard multimodal analgesia.

Settings and participants

Participants were recruited from three surgical specialties (cardiac, thoracic and abdominal) in NHS secondary care centres. They were ≥ 18 years of age undergoing non-emergency surgery and were expected to stay in hospital and be able to swallow for at least 2 days after their surgery. Participants were excluded if they were already taking gabapentinoids or other anti-epileptics or receiving planned epidural anaesthesia/analgesia.

Interventions

The trial intervention was 600 mg gabapentin – two capsules – given preoperatively and 600 mg/day (300 mg in the morning and 300 mg in the evening) given postoperatively for 2 days when clinically able to swallow following extubation, within the multimodal analgesic regimens specified by local analgesic protocols. The comparator was a placebo capsule taken at the same time points as the active tablet.

Randomisation and blinding

Participants were randomly allocated to placebo or gabapentin in a 1 : 1 ratio stratified by surgical specialty. Randomisation was via a secure internet-based randomisation system, as close to the start of surgery as possible.

Participants, the clinical care team and the research nurse(s) responsible for participant follow-up were not informed of the allocation. Gabapentin capsules were over-encapsulated so that the capsules for active drug and placebo looked identical.

Follow-up
Patients were followed up daily until hospital discharge and then at 4 weeks and 4 months after surgery.

Outcomes

Primary outcome
The primary outcome was the time from start of surgery to hospital discharge in hours.

Secondary outcomes

- Opioid consumption in the period from surgery until hospital discharge.
- Opioid consumption from discharge until 4 months.
- Acute postoperative pain assessed using the numerical rating scale (NRS) completed at 1, 4 and 12 hours post surgery and then twice daily to discharge.
- Adverse events (AEs) from randomisation to discharge and serious adverse events (SAEs) up to 4 months post surgery.
- Health-related quality of life (HRQoL) measured using the EQ-5D, five-level version (EQ-5D-5L) questionnaire and Short Form -12 (SF-12) questionnaire completed pre-randomisation (baseline) and at follow-up at approximately 4 weeks and 4 months.
- Resource use to 4 months.
- Pain measured at baseline, 4 weeks and 4 months using the Brief Pain Inventory (BPI).

Sample size
The trial was designed to provide 90% power to detect a difference of 12.5% in the proportion of participants discharged by the median LoS in each specialty (500 participants per specialty). Due to recruitment challenges in the coronavirus disease 2019 (COVID-19) pandemic, and after discussion with the funder and Trial Steering Committee, the power was reduced to 80% (340 participants per specialty).

Statistical analyses
Analyses were directed by a pre-specified statistical analysis plan. Participants were grouped according to the randomised allocation (intention to treat). Those not undergoing surgery were excluded from the primary outcome analyses.

Specialty, treatment and the specialty by treatment interaction were included in all statistical models as fixed effects. For longitudinal outcomes, interactions with time were examined. Model fit was assessed graphically. Outcomes are adjusted for baseline where measured.

Time from surgery to hospital discharge (in hours) was compared using a Cox proportional hazards model. In-hospital deaths were censored at the specialty-specific maximum observed time-to-discharge for survivors. Opioid consumption was compared using log-linear models, and mixed-effects regression was used to compare NRS scores up to 30 days and HRQoL scores to 4 months. BPI pain scores (pain severity index and pain interference index) were compared using a two-part model, one for the occurrence of pain and the other a log-linear model for the pain score when present. The incidence of one or more SAE was compared using a generalised linear model. Subgroup analyses for the primary outcome included minimally invasive versus open surgery, sex and randomisation before or after the start of the COVID-19 pandemic. An exploratory analysis adjusting NRS scores for magnesium use was also included. Results are presented as treatment effects with 95% confidence intervals with placebo as the reference category. Analyses were performed using Stata, version 17.0 (StataCorp, College Station, TX, USA).

Economic evaluation

The within-trial economic evaluation was conducted from an NHS and Personal Social Services perspective, with the primary outcome of quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L. Resource use from day of surgery to 4 months was costed using published reference costs. The area under the curve was used to calculate QALYs accrued by each participant. Missing data were imputed. The incremental cost-effectiveness ratio was derived from the average costs and QALYs in each group, producing an incremental cost per QALY gained of using gabapentin compared to placebo. Bootstrapping was used to quantify uncertainty in costs and effects.

Results

Patient screening and recruitment

Recruitment took place at seven NHS Secondary care centres. Between 12 April 2018 and 20 May 2022, 3405 patients were assessed for eligibility, of whom 2209 were excluded. Therefore, 1196 patients (cardiac 500, thoracic 346, abdominal 350) were recruited and randomised; 596 to placebo and 600 to the gabapentin group. The numbers in the two groups were well balanced across surgical specialties.

Withdrawals

Twenty-seven participants withdrew after randomisation; 1 withdrew consent for their data to be used before surgery, 10 did not receive surgery in the study and 2 had their surgery moved to a non-study hospital (operative and primary outcome data provided for one). Two withdrawals were due to clinicians deeming the participant no longer eligible and 12 were patient decisions.

Protocol deviations

The most common deviation was where participants received fewer than the prescribed six doses of trial medication or received medication outside of window (223/1195, 18.7%). The deviations were well balanced across the groups. Thirteen of 16 ineligible participants recruited to the cardiac cohort were ineligible because the surgery was not carried out via a midline sternotomy, all having surgery via a thoracotomy incision. The were two ineligible participants recruited in the thoracic and abdominal specialties.

Patient follow-up

Follow-up data at 4 weeks and 4 months were available for 1153/1196 (96.4%) and 1120/1196 (93.6%) of randomised participants, respectively.

Numbers analysed

The analysis population consisted of 1195 randomised participants, (596 placebo group, 599 gabapentin group). One participant withdrew consent prior to surgery, at which point data collection stopped. This participant was excluded. In total, 1184 participants were included in the analysis of the primary outcome (589 placebo group, 595 gabapentin group). Ten of the 1195 participants were omitted as they did undergo surgery in the study and data were unavailable for a further one who had their surgery moved to a non-study hospital.

Baseline data

Baseline characteristics were well balanced across the placebo and gabapentin groups: median age was 69 (interquartile range 60–75) and 68 (59–74) years; male sex 388/596 (65.1%) and 406/599 (67.8%); White ethnicity 585/595 (98.3%) and 589/598 (98.5%) and body mass index 27.4 (24.4–31.2) and 27.1 (24.5–30.5) kg/m^2, respectively.

Primary outcome: hospital length of stay from surgery to discharge

There was no difference in LoS stay [median 6.15 and 5.94 days in the placebo and gabapentin groups, respectively, hazard ratio for discharge gabapentin:placebo, 1.07, (95% confidence interval 0.95 to 1.20), $p = 0.26$]. The hazard ratio for discharge was similar across the three surgical specialties ($p = 0.94$). The effect of gabapentin on time to discharge was similar in the open and minimal access subgroups, between males and females and between those operated before and after the start of the COVID-19 pandemic across all specialties.

Secondary outcomes

Opioid consumption

Opioid use (intravenous morphine equivalents) *in-hospital* differed between surgical specialties ($p = 0.001$) and over time ($p = 0.010$); in the abdominal specialty, it was significantly lower in the gabapentin group in 4 of the first 5 postoperative days [range −26% (−46%, 0%) to −36% (−52%, −14%)], with no differences in the cardiac specialty ($p \geq 0.21$ across each of the first 5 days) nor in the thoracic specialty beyond day 2 [day 1–27% (−46%, 2%); day 2–30% (−48%, −5%); range days 3–5, −5% (−31%, 29%) to −24% (−46%, 7%)]. *During follow-up*, opioid use was similar in the two groups across all specialties [−15% (−40%, 21%)].

Numerical rating of acute pain

In all specialties, acute pain (higher scores) reduced over time. The difference in mean NRS scores between the placebo and gabapentin groups also reduced over time; in the first 24 hours, the mean scores at rest and on movement were lower in the gabapentin group [median NRS placebo 3 (1–5), gabapentin 2 (0–4), mean difference (MD) −0.25 (−0.42, −0.08) at rest and NRS placebo 5 (3–7), gabapentin 5 (2–6), MD −0.25(−0.44, −0.069) on movement]. Beyond 24 hours, they were similar to the placebo group [e.g. median NRS at 48 hours: placebo 2 (0–4), gabapentin 2 (0–3), MD −0.12 (−0.28, 0.043) at rest and NRS placebo 4 (2–6), gabapentin 4 (2–6), MD -0.13 (−0.30, 0.041) on movement]. The pattern was the same across the three surgical specialties ($p > 0.80$). The conclusions were unchanged when accounting for magnesium use.

Short Form -12 questionnaire physical and mental component scores

The pattern of physical component scores over time differed across the three surgical cohorts, but the difference between the placebo and gabapentin groups was similar both over time ($p = 0.53$) and across the surgical cohorts ($p = 0.47$). On average, the physical component score was 0.87 points lower (−1.71, −0.04) in the gabapentin group compared to placebo.

The difference in the mental component score between the two groups changed over time ($p = 0.056$). At 4 weeks it was on average 0.74 points higher (−0.39, 1.87) in the gabapentin group and at 4 months it was 0.55 points lower (−1.61, 0.51) in the gabapentin group.

EQ-5D

The difference between the placebo and gabapentin groups was similar at 4 weeks and 4 months ($p = 0.39$) and across surgical cohorts ($p = 0.83$). On average, the score was 0.014 points lower (−0.033, 0.0095) in the gabapentin group compared to placebo.

Brief Pain Inventory

The number of participants reporting pain at both 4 weeks and 4 months was higher in the gabapentin group compared to the placebo group in all surgical specialties. However, where pain was reported, the severity of the pain [geometric mean ratio 0.99 (0.90, 1.08)] and interference of the pain [geometric mean ratio 1.07 (0.94, 1.22)] was similar.

Adverse events

Overall, 1453 AEs were reported in 433 participants in the placebo group compared to 1488 AEs in 420 participants in the gabapentin group. Additionally, 414 SAEs were reported in the placebo group and 505 in the gabapentin group. The events reported were reflective of the different surgeries, with more cardiac disorders in the cardiac specialty, and gastrointestinal disorders in the abdominal specialty. Most SAEs were considered to be either expected with gabapentin and/or anticipated after surgery. Less than 4% were considered unexpected (14/414, 3.4% in the placebo group, 16/505, 3.2% in the gabapentin group). There were 18 deaths, 8 in the placebo group and 10 in the gabapentin group. None were related to the intervention. The number of participants experiencing at least one SAE was similar in the two groups for participants having cardiac surgery [risk difference 0.015 (−0.21, 0.05)], higher in the gabapentin group for those having thoracic surgery [risk difference 0.06 (0.13, 0.107)] and lower in the gabapentin group for those having abdominal surgery [risk difference -0.051 (−0.095, −0.008)].

Economic evaluation

Mean QALYs to 4 months were 0.247 and 0.243 in the placebo and gabapentin groups, respectively, [MD −0.003 (−0.010, + 0.003)]. Total costs were £12,634 and £13,011 in the placebo and gabapentin groups, respectively [MD +£377 (−£790, +£1519)]. The probability that gabapentin is cost-effective at a willingness-to-pay threshold of £20,000 per QALY is 0.26. Gabapentin was unlikely to be cost-effective across a broad range of willingness-to-pay thresholds explored.

Discussion

Main findings

The GAP study has shown that among patients undergoing major surgery, the addition of gabapentin (600 mg preoperatively and 300 mg twice a day postoperatively 2 days) to multimodal analgesic regimes did not result in a change in hospital LoS, opiate use, acute pain, SAEs, quality of life or resource use, and it was not cost-effective. Overall, patients who took gabapentin had a higher incidence of pain at 4 months, albeit with similar severity to the placebo group when they did have pain. Those undergoing abdominal and thoracic surgery used less opioid medication while in-hospital, but not after discharge from hospital during follow-up. The lower opioid use did not translate into significant reductions in pain, but fewer patients suffered serious adverse effect(s) in the abdominal specialty. The increased incidence of pain at 4 months in the gabapentin group was also not seen in the abdominal surgery cohort. There were no other signals of either benefit or harm.

Strengths and limitations

The main study strength is the pragmatic trial design integrated in existing usual care pathways for a number of major surgical specialties across a number of NHS sites. It is also the first trial to assess the impact of gabapentin on hospital stay, quality of life and resource use after surgery. The major limitations were that the trial does not test the application of gabapentin to other major non-body cavity surgery (e.g. joint replacement), or non-major (e.g. day-care) surgery. It also included a non-variable dose of gabapentin, and the time-period of the intervention was restricted to 2 days after surgery.

Conclusion

Among patients undergoing major cardiac, thoracic and abdominal surgery, the addition of gabapentin (600 mg pr-operatively and 300 mg twice a day postoperatively for 48 hours) to multimodal analgesic regimes did not result in a change in hospital LoS, opiate use, acute pain, or quality of life, nor was it cost-effective.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN63614165.

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