Use of Pregabalin for Postoperative Pain: Outcomes in 2 Trials

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Lyrica is not approved for postoperative pain
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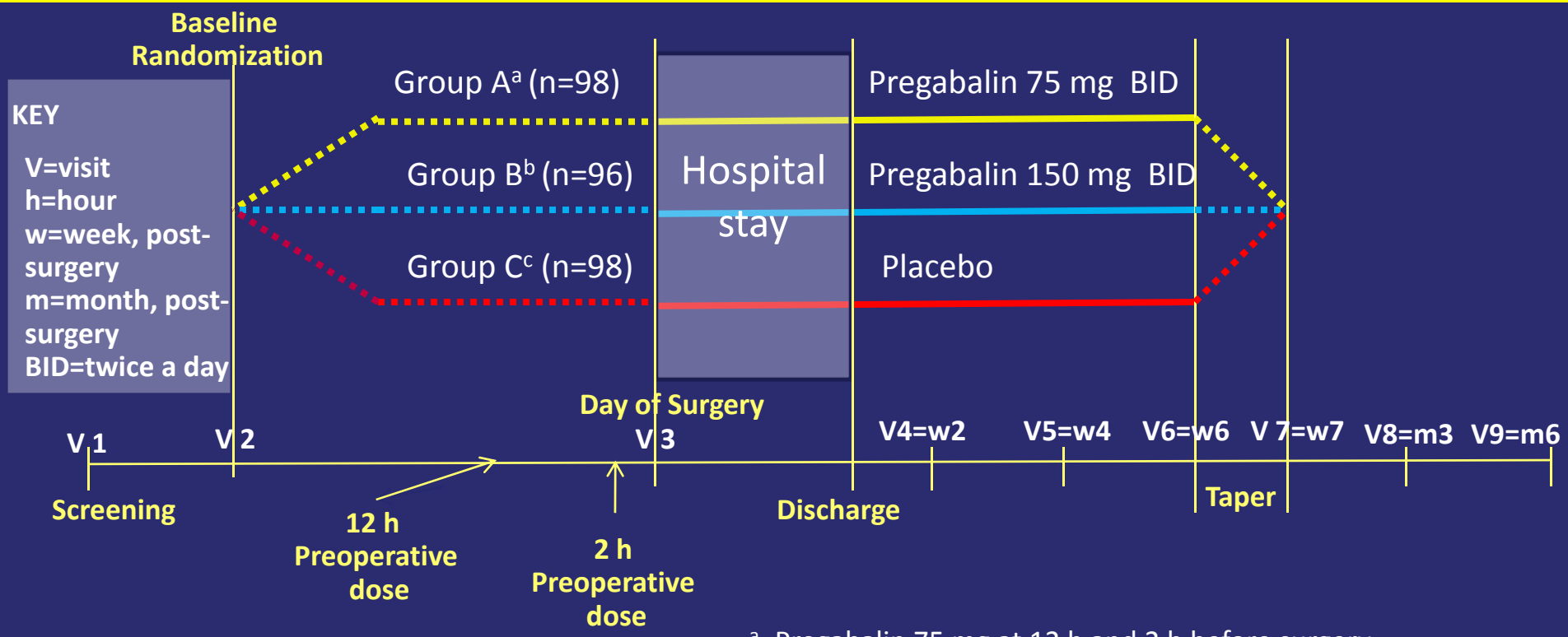
Background

- Pregabalin is an alpha-2-delta receptor modulator of voltage-gated calcium channels
- It is indicated in the US for the treatment of neuropathic pain associated with diabetic peripheral neuropathy,[1] and postherpetic neuralgia,[2] in addition to fibromyalgia[3]
- It is not currently approved for the treatment of postoperative pain
- The studies were intended to support potential registration in the US
- The efficacy and safety of pregabalin in the treatment of post-surgical pain were evaluated in 2 separate clinical trials:
  - Post-total knee arthroplasty (post-TKA) ClinicalTrials.gov identifier: NCT00442546
  - Post-inguinal hernia repair (post-IHR) ClinicalTrials.gov identifier: NCT00551135

1. Tolle et al. *Eur J Pain* 2008; 12:203-13. 2. Stacey et al. *J Pain* 2008; 9:1006-17. 3. Crofford et al. *Arthritis Rheum* 2005; 52: 1264-73.

Methods/Patients: Post-TKA Trial

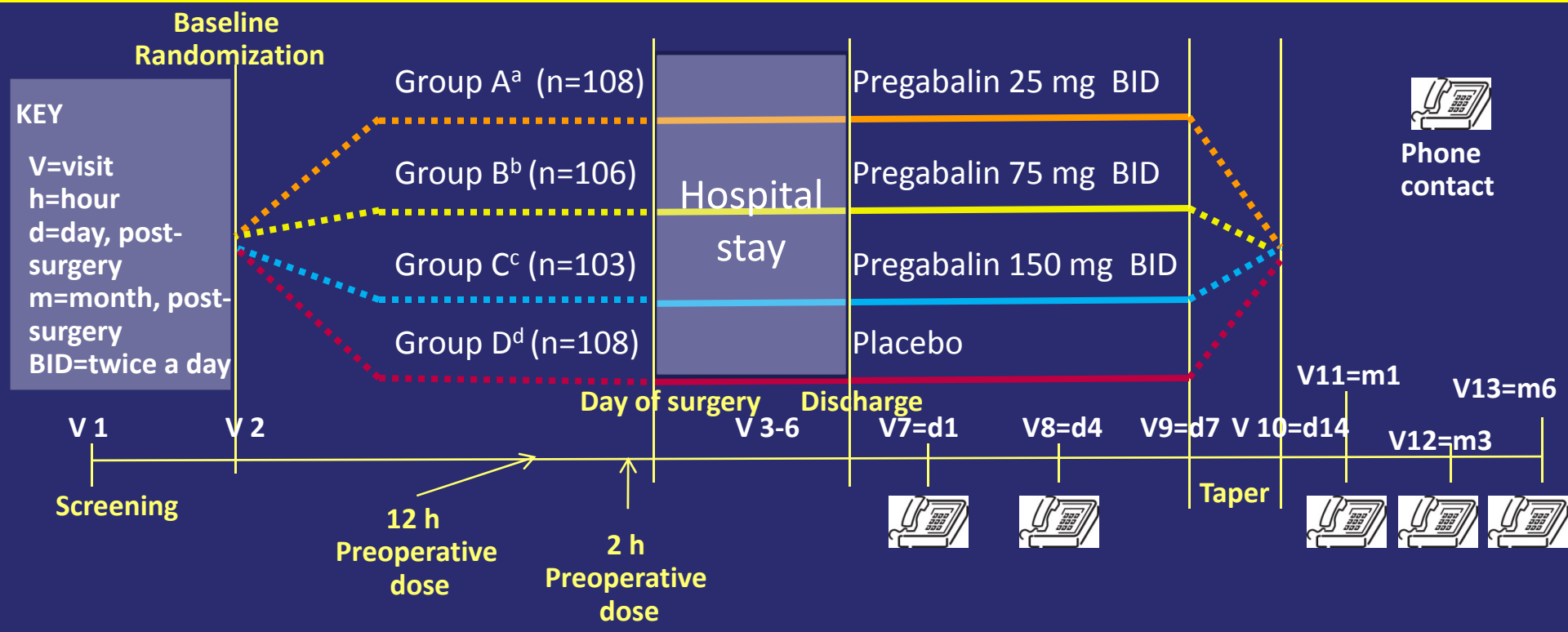


[a]=Pregabalin 75 mg at 12 h and 2 h before surgery
[b]=Pregabalin 150 mg at 12 h and 2 h before surgery
[c]=Placebo at 12 h and 2 h before surgery

Major Inclusion Criteria: Patients were adults 18 to 80 years of age with osteoarthritis undergoing TKA under regional anesthesia with or without peripheral nerve block

Major Exclusion Criteria: Patients with inflammatory arthritides, Lyme disease, fibromyalgia, chronic pain syndromes, or those reporting prior use of pregabalin (within 1 m) and/or previous participation in clinical trial (within 1 m)

Methods/Patients: Post-IHR Trial



[a]=Pregabalin 25 mg at 12 h and 2 h before surgery
[b]=Pregabalin 75 mg at 12 h and 2 h before surgery
[c]=Pregabalin 75 mg at 12 h and 150 mg 2 h before surgery
[d]=Placebo at 12 h and 2 h before surgery

Major Inclusion Criteria: All patients were men 18 to 75 years of age with mild to moderate systemic disease with or without functional limitations prior to the primary elective inguinal herniorrhaphy

Major Exclusion Criteria: Patients with emergency surgery, hernia incarceration, and those undergoing additional procedures at the time of the IHR

Primary and Secondary Endpoints

Primary efficacy endpoints:

- Post-TKA: Mean worst pain 48-h post-surgery using the 11-point NRS (0=no pain to 10=pain as bad as you can imagine)
- Post IHR: Mean worst pain 24-h post-surgery using Question 1 of the modified Brief Pain Inventory-short form (mBPI-sf)

Secondary efficacy endpoints included:

- Pre-specified intervals of patient-reported measures of:
  - current pain
  - average pain
  - pain interference, including sleep interference
- Average cumulative use of opioids were also measured at regular intervals post-operatively
- Physical functioning post-TKA was assessed by improvements in passive and active range of motion (ROM) of the operated knee and physical functioning post-IHR was assessed by reductions in movement-related pain

Statistical Analyses

- For each trial, a sample size of 100 per group was estimated to provide 90% power (α=0.05) to detect a treatment effect of 1.0, assuming a 2-sided comparison and a standard deviation of 2.2
- Efficacy analyses were carried out on a modified intent-to-treat population defined as randomized patients who were administered pre-surgery medications, with no surgical or anesthetic complications, and for whom at least 1 post-baseline safety evaluation was obtained
- The primary endpoint analyses were conducted using Analysis of Variance (ANOVA) with treatment and study center included in the models. Baseline effect was added if significant
  - Step-down procedure was applied to the TKA trial and Hochberg's multiple comparisons adjustment was used for the IHR trial
- ANOVA, Cochran-Mantel Haenszel test, Kaplan-Meier method, and log-rank test were used to evaluate secondary endpoints
- Safety analyses were conducted on all randomized patients with at least 1 dose of study medication using descriptive statistics

Results – Primary Endpoints

- Least squares (LS) mean worst pain scores recorded with pregabalin did not differ significantly from placebo for both post-TKA and post-IHR trials
  - 48-h post-TKA for pregabalin 300 mg/day (n=82) versus placebo (n=75)
    - LS mean difference, –0.34; 95% CI, –1.07, 0.39; *P*=0.362
  - 24-h post-IHR for pregabalin 300 mg/day (n=101) versus placebo (n=101) once adjusted for multiple comparisons
    - LS mean difference, –0.7; 95% CI, –1.4, –0.1; *P*=0.033; Hochberg adjusted *P*=0.067

Results – Secondary Endpoints Pain and Opioid Use

- Across both trials, there were some statistically significant reductions in self-reported postoperative pain for pregabalin 300 mg/day versus placebo (current pain; average pain; worst pain), although no consistent trends were evident
- There was an opioid sparing effect for pregabalin in both trials
  - Post-TKA:
    - Pregabalin 150 mg/day and 300 mg/day reduced the total opioid requirement versus placebo by approximately 30% and 24%, respectively, at 48 h (P=0.028; P=0.082)
    - Opioid AEs were more common in the placebo group than in treatment groups (nausea,52% vs 31%; vomiting, 26% vs 15%; pruritus, 21% vs 14%)
  - Post-IHR:
    - Pregabalin 150 mg/day and 300 mg/day reduced the total opioid requirement versus placebo by approximately 41% and 59%, respectively, at 24 h (P=0.035; P=0.002)
    - Cumulative opioid use was lower for pregabalin 300 mg/day versus placebo throughout the first 7 days after surgery (P<0.05)

Results – Secondary Endpoints Sleep Interference

- Pain-related sleep interference (NRS) LS mean was significantly reduced with pregabalin versus placebo
  - Difference at 24-h post-TKA:
    - Pregabalin 150 mg/day: –1.029; 95% CI, –2.004, –0.053; *P*=0.039
    - Pregabalin 300 mg/day: –1.810; 95% CI, –2.798, –0.822; *P*<0.001
    - Pregabalin 300 mg/day also improved sleep at 72 h (difference, –1.036; 95% CI, –1.939, –0.133; *P*=0.025) and at 96 h (difference, –1.568; 95% CI, –2.939, –0.198; *P*=0.026)
  - Post-IHR:
    - Pregabalin 300 mg/day versus placebo at Day 2, (difference, –1.01; 95% CI, –1.68, –0.34; *P*=0.003) and Day 3, (difference, –0.61; 95% CI, –1.17, –0.04; *P*=0.035)

Results – Secondary Endpoints Functional Recovery

- Post-TKA:
  - Passive ROM for the operated knee was greater with pregabalin 300 mg/day compared with placebo post-TKA at:
    - 24 h (difference, 6.532°; *P*=0.015); 72 h (difference, 7.135°; *P*=0.006); 96 h (difference, 11.173°; *P*=0.008); 120 h (difference, 17.941°; *P*=0.004)
    - There was also a significant difference at discharge (difference, 4.407°; *P*=0.022) and at Week 4 post-TKA (difference, 5.771°; *P*=0.018), although ROM of the knee decreased for the placebo group at these time-points, which may limit the interpretability of these results
- Post-IHR:
  - Patients reported less movement-related pain at 1-h post-surgery with pregabalin 300 mg/day versus placebo:
    - Pain caused by sitting (difference, –1.0; 95% CI, –1.6, –0.4; *P*=0.002); walking (difference, –0.8, 95% CI, –1.5, –0.1; *P*=0.035); and coughing (difference, –0.9; 95% CI, –1.6, –0.2; *P*=0.010)

Most Common All-Causality Treatment-Emergent AEs Occurring in ≥10% in Any Treatment Group

Adverse event, n (%)	Total Knee Arthroplasty			Inguinal Herniorrhaphy			
	Pregabalin 150 mg/day (n=98)	Pregabalin 300 mg/day (n=96)	Placebo (n=98)	Pregabalin 50 mg/day (n=108)	Pregabalin 150 mg/day (n=106)	Pregabalin 300 mg/day (n=103)	Placebo (n=108)
Nausea	29 (29.6)	31 (32.3)	51 (52.0)	21 (19.4)	18 (17.0)	14 (13.6)	22 (20.4)
Dizziness	20 (20.4)	25 (26.0)	16 (16.3)	15 (13.9)	20 (18.9)	29 (28.2)	16 (14.8)
Somnolence	24 (24.5)	22 (22.9)	20 (20.4)	24 (22.2)	25 (23.6)	25 (24.3)	28 (25.9)
Constipation	24 (24.5)	12 (12.5)	30 (30.6)	21 (19.4)	22 (20.8)	27 (26.2)	27 (25.0)
Fatigue	20 (20.4)	15 (15.6)	19 (19.4)	24 (22.2)	18 (17.0)	23 (22.3)	23 (21.3)
Pyrexia	14 (14.3)	16 (16.7)	5 (5.1)	1 (0.9)	0	1 (1.0)	4 (3.7)
Vomiting	14 (14.3)	15 (15.6)	25 (25.5)	2 (1.9)	7 (6.6)	1 (1.0)	7 (6.5)
Disturbance in attention	10 (10.2)	11 (11.5)	11 (11.2)	11 (10.2)	11 (10.4)	15 (14.6)	16 (14.8)
Pruritus	15 (15.3)	12 (12.5)	21 (21.4)	9 (8.3)	7 (6.6)	4 (3.9)	6 (5.6)
Hypotension	13 (13.3)	12 (12.5)	5 (5.1)	7 (6.5)	3 (2.8)	4 (3.9)	2 (1.9)
Insomnia	8 (8.2)	12 (12.5)	17 (17.3)	1 (0.9)	0	3 (2.9)	3 (2.8)
Confusional state	9 (9.2)	10 (10.4)	5 (5.1)	6 (5.6)	3 (2.8)	8 (7.8)	6 (5.6)
Edema peripheral	8 (8.2)	9 (9.4)	11 (11.2)	0	0	0	1 (0.9)

Discussion

- TKA:
  - While many of the primary and secondary endpoints of pain were not met, there was a significant reduction in opioid use, and improvements in passive ROM in the operated knee. These results are consistent with a single-site study by Buvanendran et al (2010)[1] assessing pregabalin post-TKA
  - The assessment of chronic pain in this trial was inconclusive – however, the study by Buvanendran and colleagues[1] did find a significant effect of pregabalin versus placebo on chronic neuropathic pain at 3- and 6-months post-surgery
- IHR:
  - Consistent with the TKA trial, there was a significant opioid sparing effect in the IHR trial
  - The assessment of chronic neuropathic pain was also inconclusive in this trial

1. Buvanendran A et al. *Anesth Analg* 2010; 110: 199-207.

Limitations

- A major limitation of these trials was the lack of standardized surgical procedures
- The results may have been confounded by variations in anesthetic and analgesic use across study centers which limits the interpretation of the results
- A challenge for all postoperative clinical RCT trials seeking to meet FDA approval in the US is to establish the efficacy of the drug while maintaining the clinical requirements of real-world patients

Conclusions

- There was no clear evidence of reductions in self-evaluated postoperative pain scores with pregabalin versus placebo
- However, pregabalin demonstrated an opioid sparing effect, improvements in pain-related sleep, increased passive ROM in operated knee and other functional improvements in comparison with placebo
- The most common AEs in the pregabalin treatment arms were nausea, somnolence, constipation, and dizziness
  - The majority of these were reported as being of mild to moderate intensity
- The results of these 2 studies offer justification for further controlled pregabalin trials to assess postoperative pain
- Additional studies are necessary to establish the full benefit of pregabalin in acute surgical settings