RESEARCH ARTICLE

# How safe and effective is oral analgesia for hip fracture patients? A prospective cohort study

Zehra Abdul Muhammad, Tashfeen Ahmad


## Abstract

**Objective:** To assess the safety and pain reduction profile of routinely prescribed oral analgesics in patients of hip fracture surgery.

**Method:** The single-centre, prospective, cohort study was conducted from June 2022 to July 2023 at the Aga Khan University Hospital, Karachi and comprised adult patients of either gender with hip fractures. The analgesics prescribed at the time of hospital discharge and 1-week follow-up were recorded along with pain and adverse effects till the 2-week post-discharge follow-up. Pain was recorded using the visual analogue scale, with the target score set at 3/10. The relationship between covariates to pain or adverse events was assessed. Possible analgesic-related deaths/adverse events, absolute risk and age-specific death rates were also calculated. Data was analysed using SPSS 19.

**Results:** Of the 133 patients, 80(60.1%) were females and 53(39.8%) were males. The overall median age was 73 years (interquartile range: 16 years). The median pain score was 4 (interquartile range: 2) and 2 (interquartile range: 2) at 1-week and 2-week follow-up, respectively. Adverse events were experienced by 83(62.4%) patients, while 1(0.75%) patient was lost to follow-up at both follow-ups. Of the remaining 132(99.2%) patients, 106(80.3%) were aged >60 years, and 26(19.6%) were aged <60 years. Sub-optimal analgesia at 1-week follow-up with high adverse events was observed after combining acetaminophen with analgesics like ibuprofen (100% and 50% of 2), diclofenac (55% and 50% of 20), meloxicam (50% and 50% of 4), celecoxib (71.4% and 42.8% of 7), tramadol (60% and 57% of 35), pregabalin (100% and 50% of 2), or gabapentin (50% and 50% of 2) respectively. There were 7(5.3%) deaths of which 5(71.4%) were analgesic-related. All 5 of 132 (3.78%) potentially analgesic-related deaths occurred among >60 years of age. Thus, in 106 patients with age >60 years, 5(4.7%) died, and the age-specific death rate was 4,717/100,000 population. The odds of adverse events increased with comorbidity ($p$=0.02). Pain score was significantly related to adverse events ($p$=0.007).

**Conclusion:** Combining acetaminophen with other analgesics did not improve analgesia, but did increase adverse events. The risk of adverse events and mortality were higher with comorbidity and older age.


**Keywords:** Adverse drug events, Analgesics, Analgesia, Hip fractures. (JPMA 75: 434; 2025)

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## Introduction

Fractures are commonly caused by trauma with devastating pain and restricted movement at the fracture site.[1] Pain management is an integral part of fracture care to prevent pain stress. Inadequate analgesia might result in serious systemic complications, like cardiac or respiratory problems, and thus increase the risk of morbidity, mortality and chances of developing chronic pain.[2-4] Timely and adequate pain control may avert these health risks.

For fracture pain control, various non-pharmaceutical options are available, including traction and injury-site immobilisation methods. Besides, surgeons recommend analgesics either alone or in combinations as per their choice, experience, pain severity, and the extent of surgery. In the available literature on analgesic treatment, several fracture pain management guidelines have been described, including the ones from the National Institute for Health and Care Excellence (NICE) and the Centres for Disease Control and Prevention (CDC), while multimodal analgesic treatment and others are also available.[5-8] All these are helpful in managing fracture pain, but, to our knowledge, there is a gap in the literature on the adequacy of analgesic response based on the population, patients' characteristics, and clinical features.

Most of the published studies have examined anaesthesia and have been conducted on the paediatric population, while some studies are ongoing with the aim of providing a better understanding of optimal pain management in adults and as per specific fracture types.[9-12] Individual patient characteristics, like age, analgesic tolerance, comorbid condition, and anatomical fracture site need further exploration to determine potential predisposing factors to analgesic-related complications.

The current study was planned to assess the safety and pain reduction profile of routinely prescribed oral

Department of Surgery, Aga Khan University Hospital, Karachi, Pakistan.
**Correspondence:** Zehra Abdul Muhammad. e-mail: zehra.abdul@aku.edu
ORCID ID: 0000-0002-6048-9042

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analgesics in patients of hip fracture surgery.

## Patients and Methods

The single-centre, prospective, cohort study was conducted from June 2022 to July 2023 at the Aga Khan University Hospital, Karachi. After approval from the Aga Khan University ethics review committee, the sample size was calculated using the World Health Organisation (WHO) calculator[13] in the light of literature according to which post-surgical pain decreases by 3.0±1.6 after tramadol-added acetaminophen administration.[14] The current study used an anticipated visual analogue scale (VAS) pain score 3.5±1.6, power 80%, significance level 5% and population variance 2.56. The sample size was inflated by 10%. The sample was raised using non-probability consecutive sampling technique. Those included were adult patients of either gender with hip fractures. Those with ankle and hindfoot fractures were excluded, and so were cases of limb amputation. Informed consent was obtained from all the patients, and those not willing to participate were excluded.

Patient data was obtained from hospital records. Oral analgesics prescribed at the time of hospital discharge and 1-week follow-up were recorded along with pain and adverse effects till the 2-week post-discharge follow-up. At 1-week and 2-week follow-ups, any clinically assessed or patient-reported adverse event (AE) or serious adverse event (SAE) that was potentially related to prescribed analgesics was documented. Pain was assessed using VAS, with score 0=no pain, 1-3=mild pain, 4-6=moderate pain, and 7-10=severe pain.[15,16] The target score set at 3. Those who did not arrive at the follow-up were contacted by phone to obtain the relevant information. Prescribed oral analgesics were stratified according to analgesia being adequate or suboptimal, and safety was assessed on the basis of AEs and SAEs.

Data was analysed using SPSS 19. Quantitative variables were reported as median with interquartile range (IQR) after applying the Kolmogorov-Smirnov test of data normality. Qualitative data was reported as frequencies and percentages. The absolute risk of potentially analgesics-related AE/SAEs, deaths and age-specific (>60 years) death rate was calculated. Linear or multiple logistic regression analysis was performed, respectively, for the relationship of age, gender, comorbid condition, and fracture type (intertrochanteric or femoral neck) to pain score at follow-ups or AE/SAE (binary, at least one AE/SAE in 2 weeks). Multiple logistic regression analysis was performed between possibly analgesics-related deaths (binary) and comorbid conditions (binary), age and gender. Binary logistic regression analysed the association between AE/SAE (binary) and VAS pain grades at follow-ups or fracture type. Multinomial regression analysis was applied for individual comorbid condition categories and morbidity-causing AEs/SAEs. P<0.05 was considered statistically significant.

## Results

Of the 259 patients screened, 48(18.5%) were not eligible, 8(3%) were not willing to participate, and 9(3.4%) patients did not undergo surgery due to financial reasons. Of the 194(74.9%) patients, 61(31.4%) had ankle and/or hindfoot fractures, and were thus excluded, while 133(68.5%) had hip fractures and formed the study sample. Of them, 80(60.1%) were females and 53(39.8%) were males. The overall median age was 73 years (IQR: 16 years). The most common cause of injury was ground-level fall 115(86.5%), followed by road traffic accidents (RTAs) 15(11.3%). The fracture type was intertrochanteric in 71(53.4%) cases, followed by femoral neck in 45(33.8%) (Table 1).

The median pain score was 4 (IQR: 2) and 2 (IQR: 2) at 1-week and 2-week follow-up, respectively. AEs were experienced by 83(62.4%) patients, while 1(0.75%) patient was lost to follow-up (LTF) for both follow-ups with no data

**Table-1:** Proximal femoral fracture types.

| Site | n (%) |
|---|---|
| Femoral head | 2 (1.5) |
| Femoral neck | 45 (33.8) |
| Intertrochanteric | 71 (53.4) |
| Subtrochanteric | 12 (9.0)–one bilateral |
| Intertrochanteric + Femoral neck | 1 (0.7) |
| Intertrochanteric + Greater trochanter | 1 (0.7) |
| Femoral neck + Greater trochanter | 1 (0.7) |

**Table-2:** Potentially analgesics-related adverse and serious adverse events at follow-ups.

| | Total events, n (%) | No event, n (%) | LTF (one patient LTF at both follow-ups) n (%) | Expired (not related to analgesics) n (%) |
|---|---|---|---|---|
| 1-week follow-up (n=133) | 74 (55.6) SAE=33 (44.5) with three expired AE=41 (55.4) | 57 (42.8) | 2 (1.5) | 00 |
| 2-week follow-up (n=130) | 51 (39.2) SAE=30 (58.8) with two expired AE=21(41.1) | 75 (57.6) | 2 (1.53) | 2 (1.53) (One expired due to dengue fever, another had sudden death while not on analgesics) |

Total combined events at follow-ups for individual patients, n=83 (62.8 of 132). One was LTF at both follow-ups, thus, excluded; LTF: Lost to follow-up, SAE: Serious adverse event, AE: Adverse event.

**Table-3:** Analgesics or their combinations prescribed at discharge and/or 1-week follow-up with AE/SAEs and VAS pain grades.

| Analgesic(s)/day dose prescribed at discharge and/or 1-week follow-up (n) | AE/SAEs | | Pain grade at 1-week follow-up | Pain grade at 2-weeks follow-up | Analgesic(s) prescribed at both follow-ups/LTF |
|---|---|---|---|---|---|
| **Tramadol + Acetaminophen** (n=36, 27.2% of 132)<br><br>AE/SAEs (n=21, 60%)<br>None (n=14, 40%)<br>LTF (n=1) | Tramadol 37.5mg + Acetaminophen 3325mg (n=3, 8.5%) | Nausea, constipation, oral ulcers, dyspnoea (n=3, 100%) | Mild (n=10, 28.5%), moderate (n=14, 40%), severe (n=6, 17.1%) (Tramadol + Acetaminophen prescribed to 30 patients at week-1) | No pain (n=3, 8.5%), mild (n=12, 34.2%), moderate(n=6, 17.1%), severe (n=1, 2.8%), LTF (n=1, 2.8%) (Tramadol + Acetaminophen prescribed to 23 patients at week-2) | n=17, 48.5%<br>LTF (n=1) |
| | Tramadol 150mg + Acetaminophen 4000mg (n=7, 20%) | Diarrhoea, dysuria, epigastric pain (n=2, 28.5%) None (n=5, 71.4) | | | |
| | Tramadol 75mg + Acetaminophen 3650mg (n=3, 8.5%) | Tachycardia, dizziness, diarrhoea, dyspnoea, restlessness (n=1, 33.3%) None (n=2, 66.6%) | | | |
| | Tramadol 150mg + Acetaminophen 3000mg (n=3, 8.5%) | Oral ulcers, hypotension, nausea, headache (n=2, 66.6%) None (n=1, 33.3%) | | | |
| | Tramadol 37.5mg + Acetaminophen 2325mg (n=5, 14.2%) | Constipation, anorexia, hypotension, drowsiness (n=1, 20%) None (n=4, 80%) | | | |
| | Tramadol 75mg + Acetaminophen 4650mg (n=2, 5.7%) | Drowsiness, dizziness, hypotension, hypoglycaemia, weakness, fatigue (n=2, 100%) | | | |
| | Tramadol 37.5mg + Acetaminophen 4325mg (n=2, 5.7%) | Vomiting, constipation, excess mucus production, anorexia, ageusia (n=2, 100%) | | | |
| | Tramadol 200mg + Acetaminophen 3000mg (n=1, 2.8%) | Drowsiness, irritability, hypotension (n=1, 100%) | | | |
| | Tramadol 100mg + Acetaminophen 4000mg (n=2, 5.7%) | Vomiting, anorexia, nausea, mood changes, drowsiness, weakness (n=2, 100%) | | | |
| | Tramadol 37.5mg + Acetaminophen 325mg (n=2, 5.7%) | Vertigo, chest pain, fatigue, drowsiness, vomiting, acute kidney injury, pneumonia (n=2, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 2650mg (n=1, 2.8%) | None (n=1, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 650mg (n=3, 8.5%) | Dizziness, hypotension, weakness, fatigue, ageusia, anorexia (n=2, 66.6%) None (n=1, 33.3%) | | | |
| | Tramadol 37.5mg + Acetaminophen 1325mg (n=1, 2.8%) | Hypotension (n=1, 100%) | | | |
| **Acetaminophen** (n=23, 17.4% of 132)<br><br>AE/SAEs (n=9, 39.1%), including one death)<br>Expired (n=1, 4.3%)<br>None (n=13, 56.5%) | Acetaminophen 4000mg (n=4, 17.3%) | None (n=1, 25.0%), anorexia, nausea, oral ulcers, drowsiness, fever, vomiting, diarrhoea, hypertension, dyspnoea (low oxygen saturation 60%), anxiety, insomnia, hypotension (n=3, 75.0%) | Mild (n=1, 4.3%), moderate (n=1, 4.3%), severe (n=1, 4.3%) | No pain (n=3, 13.0%), mild (n=15, 65.2%), moderate (n=3, 13.0%), expired (n=2, 8.6%) | n=3, 4.3% |
| | Acetaminophen 3000mg (n=5, 21.7%) | None (n=3, 60.0%) Anorexia, cough, constipation, hypotension (n=2, 40.0%) | | | |
| | Acetaminophen 2000mg (n=4, 17.3%) | None (n=4, 100%) | | | |
| | Acetaminophen 1000mg (n=8, 34.7%) | None (n=6, 75%) Expired (sudden death) (n=1, 12.5%), Nausea, (n=1, 12.5%) *One expired with sudden death not related to analgesics and one expired due to acute intestinal obstruction (possible SAE).* | | | |
| | Acetaminophen 500mg (n=2, 8.6%) | None (n=1, 50%) hypotension (n=1, 50%) | | | |
| **Diclofenac + Acetaminophen** (n=20, 15.1% of 132)<br><br>AE/SAEs (n=11, 55%<br>Expired (n=1, 5%)<br>None (n=8, 40%) | Diclofenac 100mg + Acetaminophen 4000 mg (n=14, 70%) | Anorexia, diarrhoea, constipation, hypoglycaemia, hypotension, epigastric pain, chills, abdominal cramps, drowsiness (n=9, 64.2%). None (n=5, 35.7%) | Mild (n=5, 25%), moderate (n=10, 50%) | No pain (N=4, 20%), mild (n=7, 35%), expired (n=1, 5%) | n=7, 35% |
| | Diclofenac 100mg + Acetaminophen 3000 mg (n=2, 10%) | Constipation, hypotension, anorexia (N=1, 50%) Expired with cause not related to analgesics (dengue fever) (N=1, 50%) | | | |
| | Diclofenac 100mg + Acetaminophen 2000 mg (n=2, 10%) | None (n=2, 100%) | | | |

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**Table-3:** *Continued from previous page.....*

| Analgesic(s)/day dose prescribed at discharge and/or 1-week follow-up (n) | AE/SAEs | | Pain grade at 1-week follow-up | Pain grade at 2-weeks follow-up | Analgesic(s) prescribed at both follow-ups/LTF |
|---|---|---|---|---|---|
| | Diclofenac 150mg + Acetaminophen 4000 mg (n=1, 5%) | None (n=1, 100%) | | | |
| | Diclofenac 100mg + Acetaminophen 1000 mg (n=1, 5%) | Constipation, insomnia, anxiety, epigastric pain (n=1, 100%) | | | |
| **Tramadol + Acetaminophen + Etoricoxib** (n=10, 7.5% of 132)<br><br>AE/SAEs (n=5, 50% including one death)<br>None (n=5, 50%) | Tramadol 37.5mg + Acetaminophen 325mg + Etoricoxib 90mg (n=3, 30%) | None (n=1, 33.3%)<br>Headache, swollen itchy eyes, constipation (n=2, 66.6%) | Mild (n=5, 50%), moderate (n=2, 20%), expired (n=1, 10%) | mild (n=4, 40%), moderate (n=2, 20%) | n=4, 40% |
| | Tramadol 37.5mg + Acetaminophen 4325mg + Etoricoxib 90mg (n=1, 10%) | None (n=1, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 2650mg + Etoricoxib 90mg (n=2, 20%) | None (n=2, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 3650mg + Etoricoxib 60mg (n=1, 10%) | *One (100%) expired with pulmonary embolism less likely due to analgesics (possible SAE). The patient was treated with anti-coagulants enoxaparin and tranexamic acid in-hospital while aspirin 75mg OD was prescribed at the time of discharge.* | | | |
| | Tramadol 37.5mg + Acetaminophen 2325mg + Etoricoxib 90mg (n=1, 10%) | None (n=1, 100%) | | | |
| | Tramadol 100mg + Acetaminophen 3000mg + Etoricoxib 90mg (n=1, 10%) | Hypotension (n=1, 100%) | | | |
| | Tramadol 100mg + Acetaminophen 1000mg + Etoricoxib 90mg (n=1, 10%) | Shortness of breath (oxygen saturation 82%), chest pain (n=1, 100%) | | | |
| **Tramadol + Acetaminophen + Diclofenac** (n=10)<br><br>AE/SAEs (n=7 including one death)<br>None (n=3) | Tramadol 75mg + Acetaminophen 650mg + Diclofenac 100 mg (n=3, 30%) | None (n=1, 33.3%)<br>Expired with pneumonia (possible SAE) (n=1, 33.3%), hypotension (n=1, 33.3%) | Mild (n=2, 20%), moderate (n=6, 60%), severe (n=1, 10%), expired (n=1, 10%) | Mild (n=3, 30%) | n=3, 30% |
| | Tramadol 150mg + Acetaminophen 4000mg + Diclofenac 100 mg (n=2, 20%) | None (n=1, 50%) hypotension (n=1, 50%) | | | |
| | Tramadol 37.5mg + Acetaminophen 4325mg + Diclofenac 100 mg (n=1, 10%) | None (n=1, 100%) | | | |
| | Tramadol 112.5mg + Acetaminophen 4975mg + Diclofenac 100 mg (n=1, 10%) | Hypotension (n=1, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 3650mg + Diclofenac 100 mg (n=1, 10%) | Hypertension (n=1, 100%) | | | |
| | Tramadol 37.5mg + Acetaminophen 3325mg + Diclofenac 100 mg (n=1, 10%) | Fever (n=1, 100%) | | | |
| | Tramadol 75mg + Acetaminophen 1650mg + Diclofenac 100 mg (n=1, 10%) | Hypotension, anorexia, constipation (n=1, 100%) | | | |
| **Pregabalin + Acetaminophen + Tramadol** (n=8, 6.0%)<br><br>AE/SAEs (n=4, 50%)<br>None (n=4, 50%) | Pregabalin 75 mg + Acetaminophen 650mg + Tramadol 75mg (n=3, 37.5%) | None (n=2, 66.6%)<br>Hypotension (n=1, 33.3%) | Mild (n=2, 25%), moderate (n=3, 37.5%) | Mild (n=4, 50%), severe (n=1, 12.5%) | n=2, 25% |
| | Pregabalin 75 mg + Acetaminophen 1650mg + Tramadol 75mg (n=1, 12.5%) | Anxiety, insomnia, fever 101o F (n=1, 100%) | | | |
| | Pregabalin 75 mg + Acetaminophen 4975mg + Tramadol 112.5mg (n=1, 12.5%) | Hypotension (n=1, 100%) | | | |
| | Pregabalin 75 mg + Acetaminophen 4000mg + Tramadol 100mg (n=1, 12.5%) | Hypotension (n=1, 100%) | | | |
| | Pregabalin 75mg + Acetaminophen 1325mg + Tramadol 37.5 mg (n=1, 12.5%) | None (n=1, 100%) | | | |
| | Pregabalin 75mg + Acetaminophen 3325mg + Tramadol 37.5 mg (n=1, 12.5%) | None (n=1, 100%) | | | |
| **Acetaminophen + Piroxicam/Piroxicam -beta-cyclodextrin** (n=6, 4.5% of 132)<br><br>AE/SAEs (n=3, 50%)<br>None (n=3, 50%) | Acetaminophen 3000mg + Piroxicam 20mg (n=3, 50%) | None (n=2, 66.6%)<br>Hypertension (n=1, 33.3%) | No pain (n=1, 16.6%), mild (n=1, 16.6%), moderate (n=3, 50%) | Mild (N=1, 16.6%) | n=0 |
| | Acetaminophen 4000mg + Piroxicam 20mg (n=2, 33.3%) | None (n=2, 66.6%)<br>Hypotension (n=1, 33.3%) | | | |
| | Acetaminophen 3,000mg + Piroxicam-beta-cyclodextrin 40mg (n=1, 16.6%) | Anxiety, nausea, hypertension (n=2, 100%) | | | |
| | Acetaminophen 3,000mg + Piroxicam-beta-cyclodextrin 40mg (n=1, 16.6%) | None (n=1, 100%) | | | |

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**Table-3:** *Continued from previous page.....*

| Analgesic(s)/day dose prescribed at discharge and/or 1-week follow-up (n) | AE/SAEs | | Pain grade at 1-week follow-up | Pain grade at 2-weeks follow-up | Analgesic(s) prescribed at both follow-ups/LTF |
|---|---|---|---|---|---|
| **Naproxen + Tramadol + Acetaminophen** (n=5, 3.7% of 132)<br><br>AE/SAEs n=1, 20%)<br>None (n=4, 80%) | Naproxen 1100 mg + Tramadol 75mg + Acetaminophen 650mg (n=3, 60%)<br>Naproxen 550 mg + Tramadol 75mg + Acetaminophen 650mg (n=2, 40%) | None (n=2, 66.6%)<br>Hypotension (n=1, 33.3%)<br>None (n=2, 100%) | Mild (n=2, 40%), moderate (n=2, 40%) | Mild (n=3, 60%) | n=2, 40% |
| **Orphenadrine + Acetaminophen** (n=7, 5.3% of 132)<br><br>AE/SAEs (n=3, 42.8%)<br>None (n=4, 57.1%) | Orphenadrine 100mg + Acetaminophen 1300mg (n=2, 28.5%)<br>Orphenadrine 150mg + Acetaminophen 2950mg (n=1, 14.2%)<br>Orphenadrine 50mg + Acetaminophen 650mg (n=1, 14.2%)<br>Orphenadrine 70mg + Acetaminophen 1900mg (n=1, 14.2%)<br>Orphenadrine 50mg + Acetaminophen 1650mg (n=1, 14.2%)<br>Orphenadrine 150mg + Acetaminophen 1950mg (N=1, 14.2%) | Dizziness (n=1, 50%)<br>None (n=1, 50%)<br>Hypotension, restlessness, insomnia (n=1, 100%)<br>Epigastric pain (n=1, 100%)<br>None (n=1, 100%)<br>None (n=1, 100%)<br>None (n=1, 100%) | Moderate (n=2, 28.5%) | No pain (n=3, 42.8%), mild (n=2, 28.5%), moderate (n=2, 28.5%) | n=2, 28.5% |
| **Celecoxib + Acetaminophen** (n=7, 5.3% of 132)<br><br>AE/SAEs (n=5, 71.4%)<br>None (n=2, 28.5%) | Celecoxib 200mg + Acetaminophen 4000mg (n=2, 28.5%)<br>Celecoxib 400mg + Acetaminophen 4000mg (n=2, 28.5%)<br>Celecoxib 200mg + Acetaminophen 3000mg (n=3, 42.8%) | hyponatremia, nausea, vomiting, hypotension. hypertension (n=2, 100%)<br>Fever, weakness, metabolic acidosis, polyuria, anaemia, drowsiness, anorexia, hyponatraemia (n=2, 100%)<br>None (n=2, 66.6%)<br>Anorexia, bloating, restlessness, depression, drowsiness (n=1, 33.3%) | Mild (n=2, 28.5%), moderate (n=3, 42.8%) LTF (n=1, 14.2%) | Mild (n=2, 28.5%), moderate (n=2, 28.5%) | n=3, 42.8% LTF (n=1, 14.2%) |
| **Gabapentin + Acetaminophen Diclofenac** (n=4, 3.0% of 132)<br><br>AE/SAEs (n=3, 75% including one death)<br>None (n=1, 25%) | Gabapentin 300mg + Acetaminophen 4000 + Diclofenac 150mg (n=3, 75%)<br>Gabapentin 300mg + Acetaminophen 3000 + Diclofenac 150mg (n=1, 25%) | Lower GIT bleeding, anorexia, restlessness, acidity (n=2, 50%) 66.6%. *One unspecified death (possible SAE) (n=1, 25%)*<br>None (n=1, 25%) 100% | Mild (n=1, 25%), moderate (n=2, 50%), expired (n=1, 25%) | Not applicable | Prescribed at 1-week follow-up only |
| **Acetaminophen + Meloxicam** (n=4, 3% of 132)<br><br>AE/SAEs (n=2, 50%)<br>None (n=2, 50%) | Acetaminophen 4000mg + Meloxicam 15mg (n=3, 75%)<br>Acetaminophen 3000mg + Meloxicam 15mg (n=1, 25%) | Nausea, bradycardia, hypotension (n=1, 33.3%)<br>None (n=2, 66.6%)<br>Nausea, restlessness, hypotension, insomnia, dizziness (n=1, 100%) | Moderate (n=2, 50%), severe (n=2, 50%) | Mild (n=2, 50%) | n=2, 50% |
| **Celecoxib + Acetaminophen + Tramadol** (n=4, 3% of 132)<br><br>AE/SAEs (n=3, 75%)<br>None (n=1, 25%) | Celecoxib 200mg + Acetaminophen 325mg + Tramadol 37.5mg (n=2, 50%)<br>Celecoxib 200mg + Acetaminophen 4000mg + Tramadol 150mg (n=1, 25%)<br>Celecoxib 200mg + Acetaminophen 2300mg + Tramadol 150mg (n=1, 25%) | Hallucinations, insomnia, drowsiness (n=2, 100%)<br>Nausea (n=1, 100%)<br>None (n=1, 100%) | Moderate (n=4, 100%) | Mild (n=1, 25%) | n=1, 25% |
| **Gabapentin + Acetaminophen** (n=2, 1.5% of 132)<br><br>AE/SAEs (n=1, 50%)<br>None (n=1, 50%) | Gabapentin 300mg + Acetaminophen 2000mg (n=1, 50%)<br>Gabapentin 600mg + Acetaminophen 1500mg (n=1, 50%) | Hypotension, fever, diarrhoea (n=1, 100%)<br>None (n=1, 100%) | Moderate (n=1, 50%) | Mild (n=1, 50%), severe (n=1, 50%) | n=1, 50% |

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for AE/SAE, death, or pain scores, thus was excluded from the analysis. Of the remaining 132(99.2%) patients, 106(80.3%) were aged >60 years, and 26(19.6%) were aged <60 years. There were 7(5.3%) deaths of which 5(71.4%) were analgesic-related. Two patients were LTF for either at 1-week or at 2-week follow-up (Table 2). All the patients

**Table-3:** *Continued from previous page.....*

| Analgesic(s)/day dose prescribed at discharge and/or 1-week follow-up (n) | AE/SAEs | | Pain grade at 1-week follow-up | Pain grade at 2-weeks follow-up | Analgesic(s) prescribed at both follow-ups/LTF |
|---|---|---|---|---|---|
| **Pregabalin + Acetaminophen** (n=2, 1.5% of 132)<br>AE/SAEs (n=2, 100%) | Pregabalin 75mg + Acetaminophen 4000mg (n=1, 50%)<br>Pregabalin 75mg + Acetaminophen 3000mg (n=1, 50%) | Constipation (n=1, 100%)<br>Diarrhoea, vertigo, constipation, dizziness, chest pain, heartburn, cough, frequent urination, hypotension (n=1, 100%) | Mild (n=1, 50%), moderate (n=1, 50%) | Mild (n=2, 100%) | n=2, 100% |
| **Acetaminophen + Ibuprofen** (n=2, 1.5% of 132)<br>AE/SAEs (n=2, 100%) | Acetaminophen 1000mg + Ibuprofen 200mg (n=1, 50%)<br>Acetaminophen 3000mg + Ibuprofen 400mg (n=1, 50%) | Insomnia (n=1, 100%)<br>Insomnia, restlessness, polyuria (n=1, 100%) | Not applicable | Mild (n=1, 50%), severe (n=1, 50%) | Prescribed at 2-weeks follow-up |
| **Pregabalin g** (n=1, 0.7% of 132)<br>AE/SAEs (n=1, 100%) | Pregabalin 75 mg (n=1, 100%) | Expired (n=1, 100%) *Expired due to sudden chest pain* | Not applicable | Expired before visit | Prescribed at 2-weeks follow-up |
| **Celecoxib** (n=2, 1.5% of 132)<br>None (n=2, 100%) | Celecoxib 400mg (n=2, 100%) | None (n=2, 100%) | Not applicable | Mild (n=2, 100%) | Prescribed at 2-weeks follow-up |

AE: Adverse event, SAE: Serious adverse event, VAS: Visual analogue scale, LTF: Lost to follow-up.

**Table-4:** Regression analysis for AE/SAE, pain score and potentially analgesic-related deaths with covariates.

| Regression analysis | Dependant variables | Statistical results | Co-morbid condition | Age | Gender |
|---|---|---|---|---|---|
| **Multiple logistic regression** | AE/SAE | *p*-value | 0.02* | 0.47 | 0.36 |
| | (Nagelkerke R2=0.06) | Odds ratio | 3.5 | 0.99 | 1.4 |
| | | Confidence interval | 1.2-10.2 | 0.96-1.01 | 0.67-2.94 |
| | Potentially analgesic-related deaths | *p*-value | 0.99 | 0.05 | 0.56 |
| | (Nagelkerke R2=0.2) | Odds ratio | 0.0 | 1.11 | 0.56 |
| | | Confidence interval | 0.0 | 1.00-1.24 | 0.08-3.94 |
| **Multiple linear regression** | Pain scores on VAS pain scale at week 1 follow-up | *p*-value | 0.15 | 0.32 | 0.39 |
| | (R2=0.02) | Odds ratio | 0.79 | -0.01 | 0.32 |
| | | Confidence interval | -0.3 to 1.89 | -0.04 to 0.01 | -0.42-1.08 |
| | Pain scores on VAS pain scale at week 2 follow-up (R2=0.01) | *p*-value | 0.47 | 0.3 | 0.57 |
| | | Odds ratio | 0.51 | -0.02 | -0.28 |
| | | Confidence interval | -0.9-1.92 | -0.05-0.01 | -0.7-1.27 |
| | | | **Pain at week 1** | **Pain at week 2** | |
| **Linear regression** | Fracture type (intertrochanteric and femoral neck) | *p*-value | 0.1 | 0.2 | |
| | | Odds ratio | 0.73 | 0.69 | |
| | | Confidence interval | -0.15-1.61 | -0.38-1.78 | |
| | | | **Pain at week 1** | **Pain at week 2** | |
| **Binary logistic regression** | AE/SAE | *p*-value | 0.09 | 0.007* | |
| | | Odds ratio | 1.86 | 3.55 | |
| | | Confidence interval | 0.89-3.86 | 1.42-8.89 | |
| | | | Fracture type (intertrochanteric and femoral neck) | | |
| | | *p*-value | 0.24 | | |
| | | Odds ratio | 1.58 | | |
| | | Confidence interval | 0.73-3.44 | | |
| **Multinomial regression** | Morbid condition due to AE/SAE | | Comorbid condition | | |
| | | *p*-value | >0.05 | | |

Statistically significant (*); AE: Adverse event, SAE: Serious adverse event, VAS: Visual analogue scale, LTF: Lost to follow-up.

who expired potentially due to analgesic use were >60 years of age. Thus, an absolute death risk with age >60 years (5 deaths out of 106 patients) was 4.7% and the age-specific death rate was 4,717/100,000 population.

Combining acetaminophen with analgesics like ibuprofen, diclofenac, meloxicam, celecoxib, tramadol, pregabalin or gabapentin showed AEs along with suboptimal analgesia (Table 3).

The odds of AEs increased with comorbidity ($p$=0.02), and pain score was significantly related to AEs ($p$=0.007) (Table 4).

## Discussion

In the present study, a total 5 (3.78%) patients expired from the studied patient's population possibly attributable to analgesic-related AEs. All these expired patients were aged >60 years with an age specific absolute risk of 4.7%, thus showing an increased risk of death corresponding to advancing age. The absolute risk of AE/SAE was 62.8% in the study population. The stratification of analgesics showed that combining acetaminophen with naproxen (with/without tramadol) seemed safe, and controlled pain in a majority of the cohort, but one SAE was recorded. Few reports are available on the safety of tramadol added to non-steroidal anti-inflammatory drugs (NSAIDs).[17,18] Celecoxib also seemed safe with better pain control but only 2(1.5%) patients were prescribed this analgesic, thus the finding is inconclusive. Celecoxib has been reported to be safe.[19]

The stratification of analgesics showed AEs while analgesia was suboptimal when acetaminophen was combined with either celecoxib, tramadol, diclofenac, gabapentin, ibuprofen, pregabalin or meloxicam. Most of the patients were intolerant and few expired possibly due to these analgesics. Notably, renal function or cardiovascular problems were not considered while prescribing NSAIDs. Previous studies reported similar results with suboptimal analgesia and toxicity when acetaminophen was administered with any one of celecoxib[20,21] tramadol,[22,23] diclofenac,[24] gabapentin[25] and meloxicam.[26,27] It is reported that ibuprofen combined with acetaminophen showed inconclusive treatment outcomes.[28] Pregabalin with/without acetaminophen was intolerant with satisfactory analgesia. There are reports available showing intolerance of pregabalin when administered postoperatively or at high doses.[29]

Orphenadrine with acetaminophen showed AEs in nearly half of the patients with suboptimal analgesia in the current research which is contrary to previous reports in which this combination was reported to be safe.[30] Combining etoricoxib, acetaminophen, and tramadol showed toxicity, including death, with suboptimal analgesia.

Though acetaminophen is considered safe when administered alone, the current results showed that many patients were intolerant, and one patient expired possibly due to acetaminophen. These results showed that acetaminophen toxicity in the current population should be further evaluated. There are previous reports on acetaminophen's health risks that support the current findings.[31,32]

In the current study, a positive relationship between AE/SAEs and comorbidity was observed, suggesting that prescribed oral analgesics increased the risk of side effects in patients who had underlying comorbidity. It was also observed that patients who had more pain experienced more AEs compared to the ones with better pain control. It has been reported that inadequate postoperative pain control may affect cardiac, pulmonary and renal systems, and can cause anxiety.[33,34]

The current study has limitations as no standard analgesic prescription practice was observed among the surgeons. Besides, single-centre data has affected the generalisability of the findings. Further research with larger samples and with uniformly prescribed analgesic combinations are needed to validate the findings.

## Conclusion

Analgesic combinations of acetaminophen with either ibuprofen, diclofenac, celecoxib, tramadol, etoricoxib, meloxicam, pregabalin or gabapentin seemed potentially toxic with suboptimal analgesia. Patients with comorbidity or older age were at a higher risk of experiencing AE/SAEs and deaths. Inadequate analgesia or persistent pain after analgesic treatment could increase the risk of analgesics-related AEs. A few analgesics or combinations showed better tolerance and less toxicity, but the findings remained inconclusive.

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**Author Contribution:**

**ZAM:** Concept, design, literature search, writing, data collection, analysis and interpretation.

**TA:** Data interpretation, and critical review.