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ORIGINAL ARTICLE

Comparative Analgesic Effects of Ibuprofen, Celecoxib and Tramadol after third Molar Surgery: A Randomized Double Blind Controlled Trial

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ABSTRACT

Background: This study compared the effects of ibuprofen, celecoxib and tramadol on pain after surgical extraction of impacted mandibular third molars.

Patients and methods: This double blind randomized controlled trial recruited 135 healthy subjects who required surgical extraction of impacted mandibular third molars, with a mean age of 26.51 ± SD 6.29 years. The subjects were randomized into three equal groups and given appropriate doses of each drug immediately after extraction. They continued the drugs up to 48 hours after extraction. Postoperative pain intensity was self-recorded by subjects at 4, 8, 16, 24 and 48 hours after extraction, using visual analogue scale (VAS). Data analysis involved descriptive statistics, 2-sample Wilcoxon Mann–Whitney U test and Kruskal Wallis rank test. Statistical analysis was done using intention-to-treat analysis. The mean VAS at each point of postoperative pain assessment was compared using one way analysis of variance (ANOVA) among the three groups. Statistical significance was inferred at $p < 0.05$.

Results: The mean VAS score of the celecoxib group (32.35± SD 23.96) at 4 hours was the lowest among the three groups. This was followed by the ibuprofen group with mean VAS score of 38.96 ± SD 22.30. Whereas, the subjects in tramadol group experienced the highest VAS score (53.31 ± SD 23.30) at 4 hours. There was statistically significant difference in the mean VAS scores at 4 hours after extraction when the three groups were compared ($p = 0.0039$). Celecoxib group also had the lowest mean VAS scores at 8 hours, 24 hours and 48 hours after the extraction. None of the subjects in the ibuprofen and celecoxib groups reported any adverse effect of the analgesics, whereas 47.61% of the tramadol group did.

Conclusion: Celecoxib was the most effective analgesic of the three studied drugs in controlling postoperative pain after mandibular third molar extraction in our subjects. It was closely followed by ibuprofen while tramadol was found to be the least effective.

Clinical significance: The outcomes of this study suggest that celecoxib can be prescribed for effective control of postoperative pain after third molar surgery especially in patients with peptic ulcer disease who will not tolerate the adverse effect of traditional nonsteroidal anti-inflammatory drugs. It also shows that ibuprofen can be an analgesic of choice for patients who are not at risk of gastrointestinal complications of nonsteroidal anti-inflammatory drugs (NSAIDs). Tramadol could be considered for patients with milder postoperative pain after third molar surgery.

Keywords: Celecoxib, Ibuprofen, Postoperative pain, Third molar surgery, Tramadol.

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INTRODUCTION

Surgical extraction of impacted mandibular third molar is an invasive procedure that involves trauma to soft tissues and bony structures of the oral cavity. This is accompanied by considerable postoperative inflammatory response which results in varying degrees of pain and swelling.[1,2]

The resultant pain, triggered by the release of pain mediators, has been found to be the cause of significant deterioration in oral health-related quality of life in the immediate postoperative period.[3] Acute postoperative pain following third molar surgery, if not adequately managed can also lead to restlessness, anxiety, impaired sleep and can become chronic.[3]

The management of postoperative pain is generally poor despite the development of new standards for pain management and availability of hundreds of proprietary analgesics in the market with manufacturer's claims of efficacy. However, the rational approach to acute pain management which this study sought to explore, is to use the highest quality evidence available from systematic reviews of valid randomized trials.[4-6]

Ibuprofen and celecoxib are NSAIDS that exert their actions basically through inhibition of pro-inflammatory enzymes cyclooxygenase (COX).

Ibuprofen is a non-selective traditional NSAID (tNSAID) that nonspecifically inhibits both COX-1 and COX-2, while celecoxib, a newer drug, is a selective COX-2 inhibitor.[7] COX-1, a constitutive enzyme is distributed throughout the body and is involved in the synthesis of protective prostaglandins in the gastric mucosa, kidneys and on platelets. COX-2, on the other hand, is expressed in a few specialized tissues and is only induced during inflammation.

Therefore, when COX-2 is inhibited, prostaglandin formation is blocked. This leads to prevention of inflammation and sensitization of peripheral nociceptors which are responsible for pain after third molar surgery.[8] Although effective at relieving pain and inflammation through inhibition of COX-2, tNSAIDs are associated with a significant risk of serious gastrointestinal adverse events especially with chronic use. The ulcerogenic properties of traditional NSAIDs to a large extent relate to their capacity to inhibit prostaglandin (PGE2) and prostacyclin (PGI2) through the COX-1 in the gastric mucosa.[8,9]

Tramadol is a synthetic centrally acting analgesic compound that is structurally related to codeine and morphine.[10] It is a racemic mixture of two pharmacologically active enatiomers whose analgesic effect in humans has been demonstrated to be the combined contribution of both opioid and non-opioid analgesic mechanisms.[10,11] Tramadol is a useful alternative for patients who are intolerant of the effects of NSAIDs and opioids. Respiratory distress is markedly decreased, gastrointestinal function is largely unaffected, and there is a very favourable benefit/risk ratio and drug interaction potential.[10,12,13]

Findings from studies that compared the efficacy of analgesics for managing acute postoperative pain drawn from different pain models have limitations and drawbacks due to some clinically relevant differences among the pain model.[14,15] There has not been any randomized controlled study on celecoxib, tramadol and ibuprofen among Nigerians to the best of our knowledge. This study aims to assess the effect of multiple doses of ibuprofen, a nonselective COX inhibitor, celecoxib, a COX-2 selective inhibitor and tramadol, a synthetic opioid in the control of pain among patients undergoing mandibular third molar surgery.

PATIENTS AND METHODS

The study was a double blind randomized controlled trial which was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. Ethical clearance registration number NHREC/27/02/2009a and protocol number ERC/2010/03/12 for the study was obtained from the Ethical Committee of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife, Nigeria. Written informed consent was freely obtained from each study participant following a clear explanation of the surgical procedure and study objectives. A pilot study which recruited 25 subjects that were randomized into three groups was carried out before the main study over a period of 2 months.

Sample Selection, Randomization and Blinding

A total of 135 healthy subjects aged 18 to 45 years were selected to participate in the study which was carried out in the oral surgery clinic of the dental hospital of the Obafemi Awolowo University Teaching Hospital between September 2010 and August 2011. The inclusion criteria was: subjects with at least one impacted mandibular third molar that was indicated for surgical extraction and confirmed by periapical radiographs(classified as mesioangular, distoangular, horizontal or vertical impaction),[16] absence of uncontrolled medical or systemic conditions.

The exclusion criteria was: acute infection involving the mandibular third molar in question, unerupted mandibular third molar that is deeply buried in bone, uncontrolled medical or systemic disease, history of allergy or hypersensitivity to ibuprofen, celecoxib, tramadol, amoxycillin and metronidazole, peptic ulcer disease, pregnancy or lactation and history of psychological or physical dependence on opioids as well as history of analgesic use, 24 hours before the extraction.

The appropriate doses of each of the three medications: ibuprofen tablets (Fidson Healthcare Ltd, Nigeria); Celecoxib capsules (Heinrich Mack Nachf. GmbH and Co.KG, a subsidiary of Pfizer group, Illertissen, Germany) and tramadol tablets (PT DEXA MEDICA Palembang-Indonesia) were dispensed and kept in non-transparent sealed envelopes as follow: Tablets Ibuprofen 400 mg 8 hourly, caps celecoxib 400 mg start, then 200 mg 12 hourly and tablets tramadol 100 mg 8 hourly. There were 45 of such envelopes for each of the 3 study groups. There was no inscription of name or symbol on the tablets and capsules that could reveal the identity of any of the drugs. This assisted in ensuring the blinding of the patients to the medications.

Each envelope was labeled with a medication code number according to the randomization sequence that has

been generated before the commencement of the study. The investigator was blinded to the medication patients were taking throughout the study as medication was handled by the independent observer.

Surgical Procedure

Extractions were done on out-patient basis by a single operator using the same surgical technique under 2% lignocaine hydrochloride with 1:100,000 adrenaline as the local anaesthetic agent. A three-sided mucoperiosteal flap was raised using the modified Ward's incision.[16] Thereafter, buccodistal guttering of bone was done under copious irrigation with normal saline using round surgical bur. The tooth was delivered using appropriate elevators with or without tooth sectioning as necessitated by the type of impaction. Lingual tissues were gently retracted and protected throughout the procedure. Sharp bone edges were smoothened and sutures were placed to close the wound. Hemostasis was achieved and postoperative instructions were given to the subjects. The same antibiotic regimen was prescribed to all patients: oral amoxicillin 500 mg 8 hourly and metronidazole 400 mg 8 hourly for 5 days.

Drug Administration

Patients were made to wait for postoperative monitoring in the recovery room where they were asked to pick one of the sealed non-transparent envelopes at random and the first dose of the enclosed oral medication was administered by the independent observer immediately after extraction. They were educated on how to take the remaining drugs at home and were given a telephone number of the independent observer which they called in case of any complaints related to the medications. Patients were instructed not to take any medications other than the ones already prescribed. The assigned analgesic was provided for every patient free of charge for a 48 hour period.

Postoperative Pain Assessment

Before the extraction, patients were given a visual analogue scale which comprised a horizontal line, 100mm in length with word descriptors at each end-point 0 at the left end representing "no pain" and point 100 at the right end representing "worst pain imaginable". They were then properly educated on how to record their pain intensity on the visual analogue scale by placing a vertical mark with a pen across the horizontal line of the VAS at the point they felt represented the pain they felt at intervals. Patients were then asked to record the pain intensity felt before the extraction, immediately after extraction thereafter, serially at 4, 8, 16, 24 and 48 hours after the extraction using the visual analogue scale. Patients were also asked to record any side effect or complication of the medication they felt and report to the independent observer administering the drug. Each patient was reviewed with their pain records 24 hours after the surgery, and subsequently at suture removal on the 7th postoperative day when they were also expected to submit their VAS recordings.

Statistical Analysis

Statistical analysis was carried out using Stata 10 (Statacorp College Station, Texas). Descriptive statistics was carried out for sociodemographic variables such as age, sex, marital status, occupation, income and so on. For descriptive variables that are continuous, parameters such as mean, median, minimum and maximum and measures of variability were determined. It was also determined if these variables were normally distributed using appropriate techniques. For variables that were not normally distributed, 2-sample Wilcoxon Mann–Whitney U test or Kruskal–Wallis rank test were used. Spearman's rank correlation coefficient was used to assess relationship between continuous variables. For descriptive variables that were categorical, simple frequency and percentages were determined. Statistical analysis was done using intention-to-treat analysis. The mean VAS at each point of follow-up was compared using one way ANOVA among the three groups with SNK or Turkey post hoc test when the F-test was significant. Regression methods for repeated data were used to determine the effect of other covariates in the determination of postoperative pain. Best-fit option was used to fit the model and appropriate model checking for consistency was done. Statistical significance was inferred at $p < 0.05$.

RESULTS

The study recruited a total of 135 subjects, 48 males (35.56%) and 87 females (64.44%) whose ages ranged from 18 to 45 years with a mean ± SD of 26.51 ± 6.29 years. Demographic characteristics of the subjects between the three groups were similar for age and sex (Table 1) as well as other variables describing the difficulty of surgical procedure (Table 2).

In the tramadol group, three patients failed to return the VAS form and eight discontinued their medications at different points before 48 hours postoperative period due to unbearable adverse effects of the drug.

In ibuprofen group, four patients failed to return the VAS form, two discontinued their medications 16 hours after the extraction and one patient discontinued at 24 hours after extraction. These patients claimed they

already experienced pain relief and felt further ingestion of the medication was not necessary.

In celecoxib group, only one patient discontinued the medication at 24 hours after the extraction because the patient was no longer feeling pain.

The mean VAS score of the celecoxib group (32.35 ± SD 23.96) at 4 hours was the lowest among the three groups. The Ibuprofen group was next with mean VAS score of 38.96 ± SD 22.30 whereas, the patients in tramadol group experienced the highest VAS score (53.31 ± SD 23.30) at 4 hours. There was statistically significant difference in the mean VAS scores at 4 hours after the extraction when the three groups were compared (p = 0.0039).

The mean VAS score of the tramadol group at 8 hours was 36.71 ± SD 27.2, while that of ibuprofen and celecoxib groups were 33.36 ± SD 31.01 and 27.62 ± SD 22.30 respectively. The mean VAS score of the celecoxib (19.24 ± SD 22.34) at 16 hours remained lowest of the three, followed by Ibuprofen (19.02 ± SD 22.75) and tramadol (20.62 ± SD 20.93). At 24 hours, the celecoxib group still had the lowest mean VAS score (12.67 ± SD 17.77), followed by tramadol (17.50 ± SD 20.73) and ibuprofen (21.72 ± SD 28.0).

When celecoxib and tramadol groups were compared (Graphs 1 and 2), the mean VAS scores of the tramadol group were higher than that of the celecoxib group in all the time points after extraction and there was statistically significant difference in the mean VAS scores at 4 hours after extraction between patients in celecoxib group and tramadol group (p = 0.005).

When celecoxib and ibuprofen groups were compared, the mean VAS scores of ibuprofen group were higher than that of celecoxib except at 16 hours after extraction.

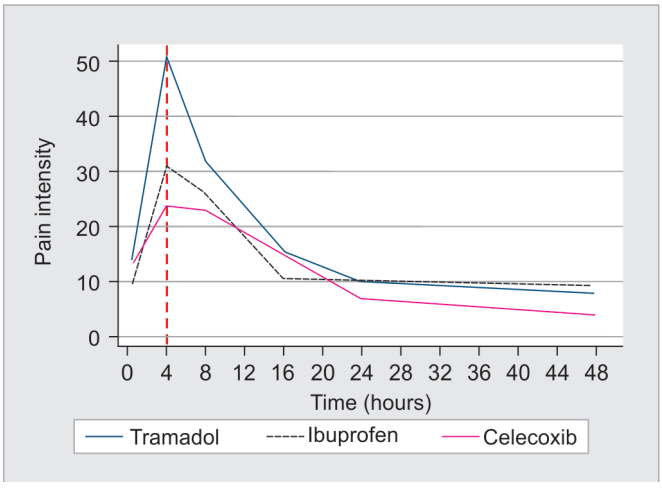
Table 1: Distribution of patients by descriptive characteristics

Variable	*Tramadol*	*Ibuprofen*	*Celecoxib*
Mean age (years)	25.75 ± 5.36	27.22 ± 7.13	26.56 ± 6.29
Sex [(freq (%)]			
Male	15 (33.33)	17 (37.78)	16 (35.56)
Female	30 (66.67)	28 (62.22)	29 (64.44)
Highest education [freq (%)]			
Primary	1 (2.22)	0 (0)	1 (2.22)
Secondary	3 (6.67)	6 (13.33)	2 (4.44)
Tertiary	41 (91.11)	39 (86.67)	41 (91.11)
No education	0 (0)	0 (0)	1 (2.22)

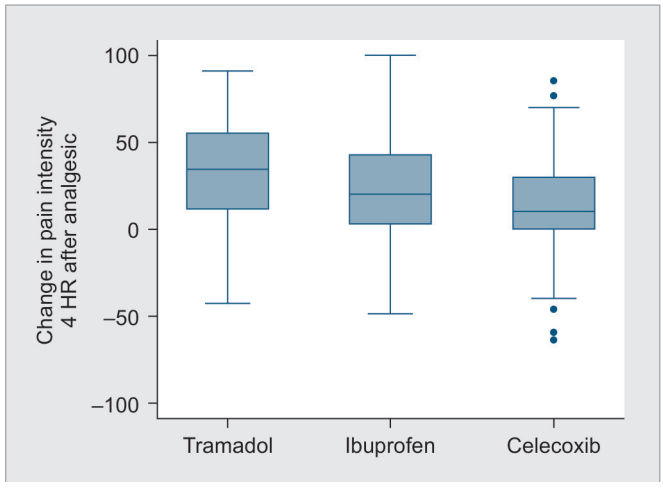
Table 2: Mean, median and inter quartile ranges of pre- and post-operative VAS scores

	Tramadol			*Ibuprofen*			*Celecoxib*			
Variables	*Mean*	*Median*	*IQR*	*Mean*	*Median*	*IQR*	*Mean*	*Median*	*IQR*	*p-value*
Before extraction	17.95	8.00	(0, 29)	17.45	5.00	(0, 35)	20.07	10.0	(1, 23)	0.86
4 hours after	53.26	51.5	(29, 73)	39.21	30.0	(16, 59)	32.77	24.0	(10, 55)	0.004*
8 hours after	36.71	32.0	(12, 52)	33.37	25.0	(10, 38)	27.62	23.0	(10, 39)	0.28
16 hours after	20.61	15.5	(3, 28)	19.02	10.0	(5, 20)	19.24	15.0	(2, 30)	0.94
24 hours after	17.50	10.0	(2, 24)	21.72	10.0	(4, 27)	12.67	7.0	(0, 20)	0.18
48 hours after	13.54	8.0	(1, 15)	17.42	9.50	(2, 15)	9.89	4.0	(0, 16)	0.25
Duration of procedure (mins)	21.71	20	(8, 40)	27.53	25	(5, 65)	22.53	20	(8, 65)	0.10

IQR–Inter quartile range



Graph 1: Comparing pain intensities (VAS scores) in the 3 groups (emphasis on 4 hours after extraction)



Graph 2: Box-and-Whisker plot comparing change in pain intensity at 4 hours after analgesic

There was no statistically significant difference in the two groups at all the time points after extraction.

None of the patients in the ibuprofen and celecoxib groups reported any adverse effect of their medications (Table 3) but 20 (47.61%) out of the 42 patients in the tramadol group reported drowsiness, vomiting, nausea and dizziness. It was also noted that 16 (80%) of the patients that experienced these adverse effects were females.

DISCUSSION

Our study compared the effects of multiple doses of celecoxib, tramadol and ibuprofen as recommended (celecoxib 400 mg start, then 200 mg 12 hourly,[17,18] tramadol 100 mg 8 hourly[19] and ibuprofen 400 mg 8 hourly)[20,21] on postoperative pain after third molar surgery over a period of 48 hours. This is unlike most dental pain model studies that compared efficacy of analgesics, where subjects received single dose or at most 2 doses of the study medications.[1,15] The design of this study therefore allowed for the assessment of the analgesic effect and safety of the drugs for a sufficient period of time, which is an important requirement for approval of an analgesic for clinical use.[22]

The maximum pain intensity felt in all the groups was recorded at 4 hours and 8 hour after extraction. This agreed with the findings of other studies that the postoperative pain after extraction is usually highest within the first 12 hours after the procedure.[23,24]

In our subjects, celecoxib was the most effective in controlling postoperative pain after mandibular third molar extraction throughout the 48 hour period. It was followed closely by ibuprofen, while tramadol produced the least analgesic effect.

Although there is paucity of information in the literature on comparative effect of Ibuprofen, tramadol and celecoxib on the control of postoperative pain after surgical extraction of mandibular third molar, Zamiri et al.[25] in a study of 41 Iranian patients compared the analgesic efficacy of ibuprofen, celecoxib and tramadol after extraction of mandibular third molar teeth.

They found out that pain severity in ibuprofen group was lower than that of celecoxib and tramadol at 4 and 8 hours after tooth extraction. They further observed that tramadol produced the least analgesic effect out of three but their findings were not statistically significant.

Table 3: Frequency of adverse effects of the drugs between groups

Variable	*Tramadol*	*Ibuprofen*	*Celecoxib*
Drowsiness	5 (11.90%)	0 (0%)	0 (0%)
Vomiting	7 (16.67%)	0 (0%)	0 (0%)
Nausea	2 (4.76%)	0 (0%)	0 (0%)
Dizziness	3 (7.14%)	0 (0%)	0 (0%)
Others	3 (7.14)	0 (0%)	0 (0%)
None	22 (52.38%)	41 (100%)	44 (100%)
Total	42 (100%)	41 (100%)	44 (100%)

The differences observed between the results of this study and that of Zamiri et al.[25] is not unexpected. The latter study was not a blinded randomized trial and like the present study, their subjects also received 600 mg of ibuprofen, a dose higher than the conventional 400 mg, which may also increase the chances of adverse effects especially if administered in multiple doses. Additionally, the drugs in Zamiri et al.[25] study were administered preoperatively (8 and 1 hour before surgery) and the results only showed the pre-emptive effects of the analgesics as contrasted with postoperative effects of drugs used in the present study. Lastly, most of the extractions in Zamiri et al. study[25] were intra-alveolar rather than transalveolar. Therefore the severity of postoperative pain felt by patients in the two studies are not comparable.

In a single dose, two-center, randomized, double blind, active- and placebo-controlled study, Cheung et al. compared the efficacy and tolerability of celecoxib 400 mg, with that of ibuprofen 400 mg and placebo following third molar surgery.[26] Their study showed that mean time to onset of analgesia with celecoxib 400 mg and ibuprofen 400 mg were rapid and comparable and significantly shorter than with placebo. They also observed that patient who received celecoxib 400 mg had a significantly longer waiting time before the need for a rescue medication than those who received ibuprofen 400 mg. Their patients also had higher pain relief scores than patients that received ibuprofen. These findings by Cheung et al.[26] is in agreement with our study.

Similarly, Mehlisch[27] and Doyle et al.[28] compared single dose celecoxib 200 mg with traditional NSAIDs such as Naproxen 550 mg and ibuprofen 400 mg .They found out that patients receiving Naproxen 550 mg and ibuprofen 400 mg had higher pain relief than those who received celecoxib 200 mg. This finding contrasts with our observation in present study where celecoxib 400 mg loading dose showed better analgesic effect than ibuprofen 400 mg. The lower efficacy of celecoxib 200 mg recorded in Mehlisch[27] and Doyle et al.[28] study can be attributed to the lower dose of 200 mg celecoxib used against 400 mg celecoxib, the recommended loading dose for acute pain that was administered to our subjects. Celecoxib at 200 mg is the recommended dose for the management of chronic pain[18] but it is inappropriately low for the treatment of acute pain as hypothesized by Cheung et al.,[26] and this may have accounted for the lesser pain relief it produced compared to the traditional NSAIDs. The administration of a loading dose of Celecoxib 400 mg used in our study can help achieve

the plasma concentrations needed for early analgesic efficacy. Therapeutic plasma levels can still be maintained by subsequent administration of the drug at the dose of 200 mg 12 hourly.

Tramadol produced the least pain relief with a considerable margin in our subjects compared with celecoxib and ibuprofen throughout the period of assessment. The result of this study demonstrated a far higher analgesic efficacy of celecoxib above tramadol. Ibuprofen also appeared to be more efficacious than tramadol.

Studies have described satisfactory analgesic efficacy of tramadol following many dental procedures and it appears its adverse effect profile is more acceptable to ambulatory surgical patients when compared with the traditional opioids.[29,30] The result of this study however did not agree with their observations. The lack of anti-inflammatory and antipyretic effects of tramadol, as well as its inability to prevent prostaglandin synthesis[10] may all contribute to its lower efficacy as seen in this study. Intravenous tramadol was found to be more efficacious and associated with milder adverse effects at equal doses when compared to the oral formulations in the management of postoperative pain after third molar surgery.[13] This observation, which is not found among NSAIDs is attributable to the reduction in the bioavailability of the oral tramadol of about 32% compared to the intravenous formulation due to first pass metabolism.[10,13]

The fact that a significant number of the subjects (47.62%) in the tramadol group experienced adverse event in this study agrees with other studies.[13,30] Collins et al.[30] reported up to 39% drop out rate of patients in their study taking tramadol (100 mg four times daily) because of adverse effects, predominantly nausea, vomiting, dizziness and drowsiness. Their study suggested that the adverse effects may be dose related because there was a remarkably lower withdrawal rate when compared with patients who took tramadol 50 mg three times daily in the same study. However, lowering the dose of tramadol will inarguably reduce its efficacy of the drug further than the outcome in our study.

CONCLUSION

The result of this study showed that celecoxib and ibuprofen are more efficacious than tramadol in the control of postoperative pain following mandibular third molar extraction. Celecoxib however produced better analgesic effect than ibuprofen when the two were compared.

Tramadol, even though demonstrated remarkable pain relieving ability after mandibular third molar extraction was the least efficacious of the three. Celecoxib and ibuprofen appeared to be generally safe for treatment of acute postsurgical pain as no adverse effect was associated with their administration for the 48 hours postoperative period. The administration tramadol in this study, was significantly associated with adverse effects.

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