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A comparative study of intravenous febrinil vial (150mg/ml) vs intravenous paracetamol (1gm/100 ml) pint formulation for postoperative analgesia

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ABSTRACT

Introduction: Paracetamol is used as an analgesic in mild to moderate pain over opioidsor NSAIDs due to lack of significant side effects. Intravenous Paracetamol is available as vial (150 mg/ml, 20 ml) and ready-to- use pint (1gm/100 ml) in market. Considering cost difference between the two formulations, we decided to conduct this study to assess analgesic efficacy against cost effectiveness between paracetamol vial and paracetamol pint.

Materials and Methods: Sixty female patients, aged 18-35 years, American Society of Anaesthesiologist physical status I–III, posted for elective or emergency caesarean section under subarachnoid block were enrolled in the study. The patients were randomly allocated into two groups of 30 patients each. In Group A, IV P aracetamol (Febrinil vial,150mg/ml, by MANISH Pharmaceuticals) 6.5 ml (1gm) from vial diluted in 100 ml normal saline infused over 15 minutes and in Group B, IV Paracetamol 100 ml pint (1 gm/100 ml, by ABBOTT Pharmaceuticals) was given over 15 minutes at the time of skin closure followed by subsequent doses at 6 hourly interval in both the groups. Patients were observed for analgesia efficacy, requirement of rescue analgesia, hemodynamic stability and side effects if any. Cost effectiveness of both formulations was noted.

Results: Demographic profile, visual analogue score, number of rescue analgesia and haemodynamic were comparable in both the groups ($p > 0.05$). No major complications were noted except nausea, vomiting, pain at injection site. But there was large difference in the cost of Paracetamol per dose between the two groups (33.66 rupees in group A vs 262 rupees in group B).

Conclusion: We conclude that paracetamol is a safe and effective treatment option in post-caesarean pain without any major side effects. Considering total dose of 4 gm/24 hrs, Paracetamol vial formulation is more cost effective and equally efficacious analgesic as compared to ready to use Paracetamol pint.

1. Introduction

Pain is important component of any surgical procedure. Inadequately treated postsurgical pain may result in adverse physiological as well as psychological consequences that may affect perioperative patient outcome.

Most commonly used analgesic drugs are opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Paracetamol is ananalgesic and antipyretic agent. Paracetamol does not consider as NSAID due nonsignificant anti-inflammatory activity. Its use is recommended worldwide as a most popular agent for the treatment of mild to moderate pain. Paracetamol is now being shown as to its efficacy against commonly used analgesics.[1] Injectable Paracetamol was introduced for intravenous (IV) use in 2002, which provides the onset of pain relief within 5-10 min, peak effect in 1hour and the duration of effect lasts for about 6 hours. Its lack of any major adverse effects, has no sedative effect, does not interfere with platelet or kidney functions. It has very rare adverse reactions (<1/10,000).[2]

Intravenous Paracetamol is available as 20 ml vial(150mg/ml, FEBRINIL by Manish pharmaceuticals),

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the cost per vial is 49 rupees from which three doses of 1 gm each can be given. The cost of ready- to - use 1% w/v Paracetamol 100 ml pint (1 000 mg/100ml, Doliprane I.V. by Abbott pharmaceuticals) is 262 rupees. These Brands of Paracetamol were selected based on availability in our hospital store supplies. Considering the cost difference between the two formulations and no study available comparing these two formulations, we decided to conduct this study to assess analgesic efficacy against cost-effectiveness between paracetamol vial and paracetamol pint.

2. Materials and Methods

After obtaining approval from Ethical Committee, this prospective randomized double blinded clinical study was carried out on 60 female patients of age 18-35 years of American Society of Anaesthesiologist (ASA) I- III posted for elective or emergency caesarean section under spinal anaesthesia. Patients with abnormal liver function tests (Serum bilirubin >2 mg%), Chronic alcoholism, chronic malnutrition, dehydration, known case of allergy to study drug were excluded from study.

After obtaining the written informed consent each patient was explained 0-10-point visual analogue scale (VAS) on a sheet of paper where (0) labelled as (no pain) and (10) as (excruciating pain).

Randomization was achieved with the help of computer-generated randomization, concealment via sealed opaque envelope technique and patients were allocated into either groups Group A (n = 30) and Group B (n = 30). The patient as well as investigator carrying out observation were blinded to group allocation.

In all patients, Peripheral venous access was secured on hand with 18G canula and preloading with Inj. Ringer Lactate 10-15 ml/kg was initiated. All the patients were premedicated with Inj. Ondansetron4 mg IV slowly. Under strict antiseptic precaution, subarachnoid block was performed in sitting position, using mid line approach with 25G spinal needle in L_3-L_4 interver tebral space. After free flow of clear CSF, injection bupivacaine 0.5% heavy, 2.2 ml (11 mg) was given. Patients were made supine immediately and sensory level up to T4 -T6 was achieved, head down tilt was given for the same if required to achieve T4 sensory level. Then caesarean section was performed by gynaecologist. Near end of the caesarean section surgery, at time of skin closure injection paracetamol was given to all patients slowly over 15 minutes and subsequent doses 6 hours apart and patients were followed for 24 hours post caesarean delivery

Group A (n:30): receiving IV Paracetamol 6.5 ml (1 gm) from vial (Febrinil,150mg/ml by MANISH Pharmaceuticals) diluted in 100 ml normal saline over 15 minutes

Group B (n:30): receiving IV Paracetamol 1gm from ready to use 1%w/v Paracetamol 100 ml pint (1% w/v, by ABBOTT pharmaceuticals) over 15 minutes

All persons involved in the study were blinded to the study medication, except the independent anaesthesiologist who filled the saline with the study solution. Both Study drug Formulations were made to look identical as sticking plastered labelled 100 ml plastic bottle to blind the observer.

The primary end-point was postoperative pain at 0, 1min, 5 min, 6 hrs, 12 hrs, 18hrs, 24hrs and intensity of pain score was assessed by using Visual analogue scale (VAS) ranging from: 0 (no pain), 10 (worst pain). Secondary end-point was the amount of administered IV rescue analgesic in the same period. All patient had option of receiving additional parenteral analgesia on request and requirement for IV rescue analgesic (injection diclofenac sodium 75 mg diluted to 10 ml) was noted.

All patients was assessed regarding hemodynamic variables (heart Rate, blood pressure). Side effects like nausea, vomiting, skin rashes, hypersensitivity reactions, pain on injection site etc were observed if any.

2.1. Statistical analysis

The sample size was calculated by power and sample size calculator. To detect a 20% difference in the primary outcome between the compared groups with a standard deviation of 25 (estimated from initial pilot observations), 80% power and 5% alpha error (two-sided); sample size of 26 per group was required. We selected 30 patients per group to compensate for dropouts. Quantitative data analysed using unpaired t-test and expressed as mean ± SD. P value <0.05 considered significant while p<0.001was considered highly significant.

3. Results

Table 1 shows demographic variables and duration of surgery were comparable in both the groups (p >0.05).

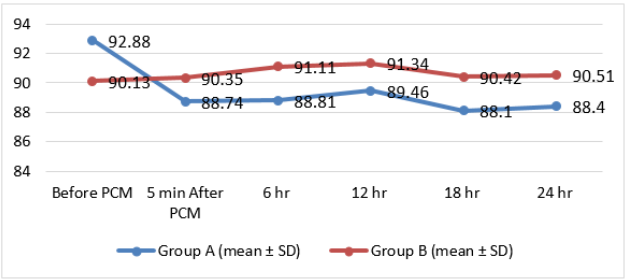

Fig. 1: Comparison of Mean arterial pressure (MAP) between two groups

Figure 1 shows Mean arterial pressure (MAP) was lower in group A as compare to group B, difference was not statistically significant.

Table 1: Demographic profile and duration of surgery

	Group A (mean ± SD)	Group B (mean ± SD)	P value
Age (yrs.)	23.83 ± 2.78	24.23 ± 2.06	0.5294
Height (cm)	157.63 ± 4.69	155.66 ± 5.37	0.1366
Weight (kg)	61.2 ± 8.41	62.76 ± 5.38	0.3941
Duration of surgery(min)	64 ± 15.5	66 ± 18.06	0.647

Table 2: VAS Score

	Group A (mean ± SD)	Group B (mean ± SD)	P value
5 min After PCM	0	0	-
6 hr after PCM	1.13 ± 1.52	1.45 ± 1.67	0.4462
12 hr after PCM	0.53 ± 0.88	0.73 ± 0.98	0.4101
18 hr After PCM	0	0	-
24 hr after PCM	0.06 ± 0.35	0	0.3131

Table 3: Number of rescue analgesic

	Group A (mean ± SD)	Group B (mean ± SD)	P value
No. of rescue analgesic	0.16± 0.37	0.23 ± 0.43	0.5237

Table 2 shows there was no statistically significant difference in VAS score between two groups ($p>0.05$).

Table 3 shows there was no statistically significant difference in number of rescue analgesia required in both the groups ($p>0.05$). In group A, 5 patients and in group B 7 patients required rescue analgesia

6.66% patients in Group A while 10% patients in Group B had complains of nausea vomiting. One patient (out of 30) in Group B had pain on injection site.

4. Discussion

Although opioids are the main drug for a cute postoperative pain control but have many side effects, so NSAIDs and paracetamol have been widely used as alternatives. Paracetamol is a stable IV form of acetaminophen and now commercially available. Major advantages of paracetamol over NSAIDs are its lack of interference with platelet function and safe administration in patients with a history of peptic ulcers or asthma.[3] Opioid-sparing effects of paracetamol make its use popular.

Effective postoperative pain management improve patient outcomes. For post-operative pain, opioids are preferred due to their efficacy but, their side effects such as nausea, vomiting, itching, and respiratory depression are main disadvantage.[4] Paracetamol is devoid of side effects that observed with the use of NSAID and opioids. It is a centrally acting inhibitor of cyclooxygenases and active metabolite of paracetamol is phenacetin, which also affords a central analgesic action cause raised pain threshold and can be administered with all routes. Intravenous Paracetamol cross blood brain barrier easily and its analgesic action starts within 15–20 min, peak by 1 h and lasts till 4–6 h.

In our study, there was no statistically significant difference in VAS score in both the groups ($p>0.05$). In 2013, Goel et al[5] studied pre-emptive a nalgesia with IV paracetamol versus IV diclofenac sodium in patients undergoing various surgical procedures found that mean pain score is higher in the diclofenac group for the initial period followed by insignificant difference in pain score for 4 hrs.

Nikoda et al[6] concluded that postoperative analgesia based on the IV infusion of PCM in a single dose of 1g (4g/day) caused a reduction in the intensity and duration of pain and the IV formulation of PCM is consider as important nonopioid components of multimodality therapy for pain in patients in the early postoperative period.

Sinatra et al[7] found the efficacy of IV PCM is superior to tramadol due to rapid onset of analgesia in orthopaedic surgeries. IV PCM 1gm, administered in patients with moderate to severe pain after orthopaedic surgery provided rapid and effective analgesia. They found IV PCM significantly reduced morphine requirement over the 24-h period.

Dejonckheere et al[8] compared IV tramadol with Paracetamol for postoperative analgesia following thyroidectomy and found that Paracetamol is a good alternative to nonsteroidal anti-infl ammatory agents with less adverse effects. Tramadol is safe and less respiratory depressant when compared to other strong opioids. In the Hoogewijs' study,[9] patients had considerably significant $PaCO_2$ in the tramadol compared to the paracetamol group.

Kela et al[10] studied the efficacy of paracetamol versus tramadol in the postoperative period in cardiothoracic surgery and found that 10% of the subjects in paracetamol group and 13.3% out of total cases in tramadol group suffered nausea and vomiting which were comparable. In

Table 4: Perioperative side effects

	Group A	Group B
Nausea	2	2
Vomiting	0	1
Pain on injection	0	1

Table 5: Average cost of analgesic treatment

	Group A (Rs.)	Group B (Rs.)
Cost per PCM dose	33.66	262
Cost of 4 gm PCM dose	134.64	1048

our study, there was no significant side effect was found except 2 patients in each group had nausea, 1 patient in group B had vomiting and 1 patient in group B had pain on injection.

In our study, there was no statistically significant difference in number of rescue analgesia required in both the groups ($p>0.05$), suggest that paracetamol provide adequate postoperative analgesia. Cattabriga et al[11] compared paracetamol verses tramadol and concluded that paracetamol is better especially when used against background tramadol analgesia in postoperative median sternotomies.

Certain clinical studies suggest that ready to use 1% w/v IV Paracetamol is likely to cause hypotension in intensive care unit settings which might be due to individual effect of the stabilizing agent Mannitol used in their study drug formulation of 1 gm PCM.[12–14] Regarding haemodynamic parameters, in our study Mannitol-free IV Paracetamol was used. Mean arterial pressure was lower in group A as compare to group B but the difference was not stastically significant and neither group required any interventions for the same. Lower MAP in Group A might be due to benzyl alcohol used as preservative in Febrinil vial. Our primary aim of study was to compare cost-effectiveness against analgesic efficacy in both groups. So further study with large sample size would be required to compare hemodynamic parameters in both the groups.

The cost of Febrinil vialused in Group A is 49 rupees from which three doses of 1 gm each can be given making it 16.33 per dose. The cost of ready- to-use 1% w/v Paracetamol 100 ml pint (1 000 mg/100ml, Doliprane I.V. by Abbott Healthcare) is 262 rupees. COST PER PCM DOSE in Group A (49/3 =16.33+17.33 as cost of 100 ml NS pint) comes around 33.66 rupees while the same for Group B would be 262 rupees, along with equal analgesic efficacy and side effect profile. It suggests that Febrinilvial group is highly cost-effective as compared to ready-to-use pint formulation without much trouble involved in preparations.

5. Conclusion

We conclude that paracetamol is a safe and effective treatment option in post-caesarean pain without any major side effects as compare to opioids and NSAIDs. Paracetamol vial is very economic and cheap option with same analgesic efficacy as compare to paracetamol pint.

6. Source of funding

None.

7. Conflict of interest

None.

References

1. Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. *Int J Clin Pharmacol Ther*. 2004;42:50–57.
2. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen) Drugs. 2009;69:101–113.
3. Jozwiak-Bebenista. Paracetamol: mechanism of action, applications and safety concern. *Acta Poloniae Pharmaceutica Drug Res*. 2014;71:11–23.
4. Benyamin R. Pain physician. Opiod complication and its side effect. 2008;11:5–20.
5. Goel P, Kothari S. Pre emptive analgesia with iv paracetamol and iv diclofenac sodium in patients undergoing various surgical procedures. 2013;4:3294–3300.
6. Nikoda VV, Makarova VV, Maiachkin RB, Bondarenko AV. Clinical aspects of analgesia with intravenous paracetamol in the early postoperative period. *Anesteziol Reanimatol*. 2006;6:54–58.
7. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiol*. 2005;102:822–831.
8. Dejonckheere M, Desjeux L, Deneu S, Ewalenko P. Intravenous tramadol compared to propacetamol for postoperative analgesia following thyroidectomy. *Acta Anaesthesiol Belg*. 2001;52:29–33.
9. Hoogewijs J, Diltoer MW, Hubloue I, Spapen HD, Camu F, Corne L. A prospective, open, single blind, randomized study comparing four analgesics in the treatment of peripheral injury in the emergency department. *Eur J Emerg Med*. 2000;7:119–123.
10. Kela M, Umbarkar S, Sarkar M, Garasia M. Comparative study of efficacy of IV paracetamolvs IV tramadol for postoperative pain relief after cardiac surgery. *Bombay Hosp J*. 2011;53:582–586.
11. Cattabriga I, Pacini D, Lamazza G, Talarico F, Bartolomeo RD, Grillone G. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. *Eur J Cardiothorac Surg*. 2007;32:527–531.

12. Chiam E, Weinberg L, Bellomo R. Paracetamol : a review with specific focus on haemodynamic effects of intravenous administration. *Heart, Lung, Vessel*. 2015;7(2):121–132.
13. Duncan CN, See J, Baker S. Centrally administered parental paracetamol: A potentially underreported cause of haemodynamic instability within the adult intensive care unit. *Aust Crit Care*. 2012;25:131.
14. Jefferie S, Saxena M, Young P. Paracetamol in critical illness: a review. *Crit Care Resusc*. 2012;14:74–80.

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