MECHANISM OF ACTION, CELLULAR TARGETS AND CLINICAL IMPORTANCE OF ANALGESIC THERAPY IN POSTOPERATIVE PEDIATRIC PATIENTS: A BRIEF OBSERVATION

ABSTRACT

Pain is a distressing sensation that has the potential to induce changes in multiple organ systems, especially in pediatric patients following surgical procedures. Efficient pain management is of the utmost importance for patients who wish to reduce or eliminate pain and distress with minimal adverse effects. The objective of this review is to investigate the clinical outcome, cellular targets, and mechanism of action of pain relief treatment in pediatric surgical patients after an operation. The literature search for this review was performed by accessing the Pubmed and Google Scholar databases; as a result, thirty publications were obtained for use as references. In compiling this review, the authors have categorized analgesic pharmaceuticals into three distinct groups: NSAIDs, opioids, and acetaminophen. In accordance with the review's stated objective, three distinct indicators are employed to compare these categories. This succinct investigation revealed that a consensus among clinicians and researchers was reached regarding the optimal strategy for managing postoperative pain in children. It was concluded that acetaminophen should be the initial course of treatment, followed by nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids being reserved as the last choice.

Keywords:Analgetictherapy,Pediatricsurgery,post-operativemanagement.

1.INTRODUCTION

Paininchildrenisidenticaltothatinadultsandcanharmthebody. Anticipating andtreatingpediatricpainiscritical.Anunpleasantexperiencelikepain canaffectallphysiologicalsystems.Paincanbepreciselyquantifiedinchildren utilizingage-specificpainscoringsystems.Analgesicsshouldbeusedearlyandin sufficientamountsto work.A multimodal approachcombiningmilderanalgesicsand localizedblockscancontrolpainandpreventseveresideeffectsfrompotent analgesics.Recentadvancesinanalgesicpharmacologyallowforbroadusewithminimaladverseeffects.The use of various analgesics should be done early and in adequate doses for them to be effective. The use of multimodal approach with weaker analgesics along with regional blocks is an effective modality to control pain and prevent severe adverse effects associated with higher doses of potent analgesics.[1]Painalleviationhasphysiologicalbenefits,thereforemonitoringitisbecomingakeypostoperativequalitymeasure.Painmanagementaftersurgeryaimstorelievediscomfortwithminimalsideeffects.[2,3]

Postoperativepaintherapyiscrucialforhospitalsformanyreasons.Proper therapyaffectspatientcare,hospitalcosts,andcomorbidities.Acutepostoperative

painremains a barrier formodernmedicine despite pharmacological and technologicalimprovements.However,acutepostoperativepainshouldbetreated basedontheintensityofthesurgicalprocedure,theanalgesics,andadequate combinationsthatenhanceanalgesiceffectsratherthansideeffects,aswellas local and regionaltechniquesassociatedwiththesurgicalsite.[4,5]Thisstudyaimstoinvestigatethemechanismofaction,cellulartargets,andclinicaloutcomeof analgetictherapyinpost-operativepediatricsurgicalpatients.

2.METHODOLOGY

Theliteraturesearchinthisreviewwascarriedoutusing Pubmedand GoogleScholardatabaseswiththreemainkeywords:pediatricsurgery,analgetic therapy,andpost-operativemanagement.Thearticleswereselectedbasedon language,typeofpublication,suitabilityofmethods,casecharacteristics,exposure, andoutcome.Allreferencesthatmatchtheinclusioncriteriaareprocessedusing theMendeley®citationmanager,whereas30articlesareobtainedasreferences. In thisreview,authorsincludethreetypesofanalgeticdrug:Acetaminophen,NSAID, andopioidswiththreeindicatorsofcomparison:Mechanismofaction,cellular targets andtheclinicaloutcomeofthepatient.

3. RESULTSANDDISCUSSION

Acetaminophen

- Mechanismofaction

Paracetamolasthemostcommonuseacetaminophendrugisafirst-line oral analgesicfor long-termusage.Acetaminophen is extensively utilized in children due to its well-established safety and efficacy. While the likelihood of children experiencing toxic reactions to acetaminophen is often lower than in adults, intentional overdoses can nevertheless lead to severe events in pediatric patients. Occasionally, acetaminophen poisoning can occur due to unintentional incorrect dosing or the failure to identify children who are more susceptible to it, even when they have been given the recommended quantities of acetaminophen. Due to the generic nature of the symptoms of acetaminophen intoxication, the diagnosis and treatment of inadvertent cases of toxicity are more likely to be delayed. This statement outlines many circumstances and factors that might lead to acetaminophen poisoning, excluding cases involving deliberate self-harm.Children'sparacetamoluserequiresspecificattentionandage-appropriatedosage,unlikeadults'.Paracetamolmetabolismdeterminestoxicity,notably hepatotoxicity,hencechildren'sdosageisbasedonthis.Younger childrenusethesulfation pathwaytoeliminateparacetamol,whichismatureatbirth,whiletheglucuronidationpathway takestwoyearstomature.Inhumans,paracetamolismetabolizedintheliverthroughglucuronidation(50-60%),sulfation(25-30%),andoxidation(<10%).Centralfunctionofparacetamolisitsstimulationofdescendingserotoninergicpathways,whichreducepain.Invivotestsonanimalsandhumansvalidated thisnotion,showingthatthisdrug'scentralantinociceptive impact involves the 5-HT3 subtype of serotoninreceptors.[6,7]

- Cellulartargets

  Themechanismsofacetaminophen's clinical selectivity remainunknown. TraditionalNSAIDsblockorchangetheactivesiteofcyclo-oxygenase,however acetaminophenmaynot.Twomaintheoriesexist.First,acetaminophenmay preferentiallyblockacentralnervoussystemcyclooxygenaseisoform,maybe thecaninebrain'sputativecyclooxygenase-3.Second,acetaminophenmay impedecyclo-oxygenaseactionbyconvertingitsactiveoxidizedformtoan inactiveformratherthanbindingtoitsactivesite.Thus,lowperoxide concentrationsmakeacetaminopheninhibitionmoreeffective.Thistheory explainsacetaminophen'snerve-specifictherapeuticselectivity.Nerves,which aresensitive to intracellular oxidants, actively minimize oxidation. The inflammatorylocationmayhavehighoxidantlevels,makingacetaminophen's lowering effects ineffective. Acetaminophen preferentially inhibits cyclo-oxygenaseactivityinendothelialcellsbutnotplatelets,andincreasing intracellularperoxidelevelspreventsitsinhibitoryeffects.[8]

  Anotherpossibilityforcellularselectivityinacetaminophenresponseis thatthedrug'smetabolicdestinychangesamongcells,whichcouldaffectits efficacybyforminganactivemetaboliteoracceleratingdruginactivation. Acetaminophenbiotransformationdataisplentifulandsuggestsselectivity. Acetaminophenismetabolizedintheliverbyglucuronidationandsulfate conjugation.Acetaminophenisdeacetylatedtoproducep-aminophenol,a powerfulnephrotoxicant.Substanceofp-aminophenolinhibitsthromboxaneA2 productioninwashedplateletsmorethanacetaminophen,basedonthisand evidencethatitinhibitsPGHSintheratrenalmedulla.Thesefindingsprovidea clearrationalefordeterminingtheextentofacetaminophendeacetylationin relationtocellularselectivity,buttheroleofcell-ortissue-specificdeacetylation inclinicalbehaviorremainstobeexplored.Arecentstudysuggeststhat acetaminophen'sanalgesicqualitiescomefromadownstreammetaboliteofp-aminophenol.Additionalresearchisneededtoprovethatthismetabolic pathwayforacetaminophenisnecessaryforitsanalgesiceffectsandthat humanshavesuchpathways.[9]

- Clinicaloutcome

  Acetaminophencandamagetheliverinlargedoses,howeverliver failureriskdependsonhealthandotherfactors.Becauseanintricatesystemof intra-andextracellularmolecularsignalingregulatesAPAP-inducedliverinjury andrecovery,weaimtoquantifytheimportanceofspecificmodulesin determiningtheoutcomeafteranAPAPinsultandofpotentialtargetsfor therapiesthatmitigateadversity.[10]Becauseitinhibitsprostaglandinsynthesis, acetaminophenhasextremelyselectiveanalgesicandantipyreticeffects. Arachidonicacid-derivedPGsarekeymediatorsofinflammation,fever,and discomfort. A practical investigation showed that intraoperative IV acetaminophenwas safeandbeneficialfor postoperativepainfollowingpediatric skinlaserirradiation.Inthatstudy,theacetaminophenIVgrouphadlowerpain levelsthantheplacebogroupupto2hourspostoperatively,exceptfor emergence.[11]

Non-SteroidAntiInflamatoryDrugs(NSAID)

- Mechanismofaction

Non-steroidalanti-inflammatorydrugs(NSAIDs)areutilizedfortheir powerfulanalgesic,anti-inflammatory,andantipyreticproperties.NSAIDswork by inhibiting COX enzyme, which biosynthesizes prostaglandins and thromboxane. Fever,pain,andinflammationaremediatedbyPGs andTXs.The pathophysiologyofmanydiseasesinvolvesinflammation.PGs,coagulation cascade-derivedpeptides,IL-2,IL-6,andTNFareaffectedbyNSAIDs. Arachidonicacid-derivedprostanoidspromoteinflammation.[12,13]

Theimmunesystemisdirectlyactivatedbysurgicalinjurythroughthe bindingofdanger-associatedmolecularpatternstopatternrecognitionreceptors intheinnateimmunesystem.Additionally,theneuroendocrinesystemis indirectlyactivatedthrough the hypothalamic-pituitary-adrenal axis. Upon activation,acascadeofhormones,cytokines,chemokines,andprostanoidsare producedinordertorestorethebody'sinternalbalance,promotetissuehealing, andcombatinfections.Anti-inflammatorynonsteroidalanti-inflammatorydrugs (NSAIDs)maybebeneficialforthisconditionastheyinhibitthesensitivityof boththeperipheralandcentralnociceptivepathways.Ibuprofen,diclofenac, ketorolac,naproxen,andflurbiprofenwereemployed,howeverCOX-2inhibitors shownagreaterreductioninpostoperativeanalgesicconsumptioncomparedto nonselectiveNSAIDs.[14]

- Cellulartargets

NSAIDsarehighlyeffectiveanalgesicsandareamongthemost commonlypurchasedmedications.Itisnecessarytoinvestigatethemolecular interactionsthatareresponsibleforboththephysiologicalactivityandthe detrimentaleffectsofthesesubstances.Ibuprofen,naproxen,anddiclofenac, which are widely used NSAIDs, have an interaction withdimyristoylphosphatidylserine,aprominentphospholipidfoundineukaryotic cells.Fourier-transforminfraredspectroscopy(FTIR)anddifferentialscanning calorimetry(DSC)areemployedtoobservethechangefromgeltoliquid crystallinephaseoftheacylchains,bothintheabsenceandpresenceofthe NSAID.TheinteractionsbetweenNSAIDsandfunctionalgroupsintheDMPS spectrum,suchastheestercarbonylandphosphatevibrationalbands,are detectedandrecordedusingFourierTransformInfraredSpectroscopy(FTIR)in reflectionmodewithAttenuated Total Reflection (ATR) technique. The thermodynamicsoftheinteractionbetweenNSAID-DMPSliposomesare assessedusingisothermaltitrationcalorimetry(ITC)andFörsterresonance energytransfer(FRET). Thedataindicatethat theNSAIDinteractswith thislipid inaspecificmanner,whileexhibitingdistinctdifferencesinotherparameters. Thisprovidesacomprehensiveunderstandingoftheinteractionprocesses.Our investigationrevealedthatNSAIDssuchasibuprofen,naproxen,anddiclofenac causedthedestabilizationofDMPSbilayers,resultingindetrimentaleffectson theirthermodynamicproperties.Drug-membraneinteractionis influencedby multipleaspects.Hydrationisessentialforthestabilizationofbilayers.The presenceofahydrationshellandthearrangementoflipidscanhaveanimpact oncellmembranes,influencingtheirsemipermeableproperties,therateand efficiencyofcelldevelopment,andtheactivityofenzymeslinkedwiththe membrane.[15]

- Clinicaloutcome

Ibuprofenisthemostextensivelyresearchedandutilizednonsteroidal anti-inflammatorydrug(NSAID)inchildrenfor thetreatmentofsudden pain,and itisthesoleNSAIDauthorizedforuseinchildrenasyoungas6months.Allof thestudiesonibuprofenexaminedadverseevents(AEs)andotherfactors relatedtosafetyandtolerability,suchasnausea,vomiting,drowsiness,and dizziness.[16]Theidealpediatricibuprofendoseis10mg/kgbodyweightevery8 h,withthemaximumsingledoseanddailydosebeing800mgand2400mg, respectively.Severeibuprofentoxicityinchildrenatdoseslessthan100mg/kg byhistorythroughouttreatmentisrare.Morethan400mg/kgbodyweightcan causeseriousorlife-threateningtoxicitiesincludegastrointestinalhemorrhage, thrombocytopenia, pulmonary edema, severe acute kidney failure, and metabolicacidosis.Sincethereisnoantidote,mainsupportivemeasures should beused.[17]

NSAIDshavemanyadvantageanddisadvantageduetotheorgan system.Intheurinarysystem,NSAIDsinhibitkidneyCOX-1andintravascular volume-dependentinducibleCOX-2.WhileCOX-1controlsglomerularfiltration rateandrenalhemodynamics,COX-2controlssaltandwaterexcretion.Inthe nervoussystem,NSAIDsmaydelayAlzheimer's.InhibitingCOX-2disruptsthe β-amyloidcascade,whichsuppressesmemoryandsynapticplasticity.[18] Moreover, NSAIDscanaffect theGIsystembydeterioratingthisprocess.These harmscanbecausedbyPGornon-PGmethods.Agastriclesioncausedby increasedmucosalpermeabilityandmyeloperoxidaseactivityincreasesgastric hypermotility.Inthe cardiovascularsystem,selectiveCOX inhibitorslowerPGI2, whichisessentialforendothelialcellvasodilationandplateletinhibition, increasingtheriskofthrombosis.PGI2andTXA2,avasoconstrictor,can becomeimbalanced,causingplateletaggregationandthrombusdevelopment.[12]

Inthegeneralpopulation,0.3%ofadultsand0.5%ofchildrenhave hypersensitivityreactionstoNSAIDs.Ibuprofenwasthemostcommonly implicatedNSAID(7,6%ofcases).Treatmentdurationanddrugdosesshould befrequentlyassessedandmanufacturerorexpertcommitteemaximumdose limitsandotherguidelinesfollowed.ThemedicalteamshouldstartNSAID medicationwiththelowestage-orweight-baseddosetoimprovesafetyin newbornsandchildren.BecauseNSAIDsareusedbyasignificantnumberof children,hypersensitivityshouldalwaysbeconsideredasadrug-induced adverseeventthatmustbemonitoredandhandled.[19–21]

Opioids

- Mechanismofaction

Opioidsaffecttheafferentandefferentpainpathways.Theyblockpain transmission from primary afferent to ascending neuronesby lowering neurotransmitterrelease.KþandCa2þchannelsplayamajorroleinthese processes,withactivationincreasingKþeffluxandhyperpolarization,while inhibitiondecreasesCa2þinfluxandlimitstransmitterrelease.Second-to-third-ordertransmissionanddescendinginhibitorycontrolactivitiesareenhancedby reducingGABAergicinhibitorytransmission.PlasticityexistsinNOPreceptor andpainprocessing.[22]NOP,MOP(m),KOP(k),andDOP(d)areclassical opioidreceptorsaccordingtoIUPHAR.AllfourG-protein-coupledreceptors

haveaseven-transmembranetopology.Insteadofdirectlycommunicatingwitheffectorproteins,G-protein-coupledreceptors(GPCRs)conveythemessage. MOPwithmorphineclosesvoltage-sensitivecalciumchannels(VSCCs), stimulatespotassiumefflux,hyperpolarizescells,andreducescyclicadenosine monophosphate(cAMP)productionbyinhibitingadenylylcyclase.Allfour receptorsubtypespreferentiallycoupletoinhibitoryG-proteins.Thisdecreases neuronal cell excitability, reducing nerve impulse transmission and neurotransmitterrelease.[23]

- Cellulartargets

  Numerousphysiologicalfunctionsdependonopioidreceptors,whichare widelydistributedinthebody.Theseincludecentralandperipheralnervous systempainsignaling,reproduction,growth,breathing,andimmunological response. Physiologically and pathophysiologically, opioid receptors are importantintheGItract.GPCRsaretargetsforaboutone-thirdofFDA-approved blockbuster medications, including analgesics, antihistamines, neuroleptics,andnumerouscardiovasculartherapies.Theopioidreceptorfamily iskeyGPCR.MOP,DOP,andKOPareprototypicalnaloxone-sensitiveopioid receptors.Thisfamilyalsoincludesthenonclassicalnociceptin/orphaninFQ (N/OFQ)receptor.Naloxonedoesnotaffectthisreceptor.Opioidsbindto Gi/Go G-proteins,causingneuronhyperpolarization,closingvoltage-gatedCa2þ channels, and inhibiting adenylyl cyclase to reduce cyclic adenosine monophosphate formation and membrane repolarization. The b-arrestin pathwayinhibitssignaling.Thesecoordinatedcellularactivitiesallowallfamily memberstoproduceanalgesia(anti-nociceptioninnon-humans)tovaried degreesandlocales.G-proteinandindependentb-arrestinpathwayslinkopioid receptorstomitogen-activatedproteinkinasessuchESRPK,p38,andJun Nterminalkinase.Allmembersofthefamilycanprovideanalgesia,butMOP receptoragonistsarethemainstayintheclinic,withsomedevelopinginstances addressednext.Thelistincludesmorphine,fentanyl,andoxycodone.Opioids havemanysideeffects,includingventilatorydepression,nauseaandvomiting, constipation,tolerance,anddependency.Tolerancecausesdoseescalation (particularlyinpalliativecare)anddependence,whichisassociatedto prematuredeathandcrimeglobally.[24,25]

- Clinicaloutcome

  Studies suggest non-opioid medications are equally effective in controllingpost-operativepainafterpediatricherniorrhaphycomparedtoopioid medications.Routineopioidadministrationdoesnotappeartopositivelyaffect postoperativepainmanagementinthispopulationandisassociatedwitha higherrateofmedicationrelatedsideeffects.Moststudysuggeststhatopioid prescriptionsaremorelikelytocauseharmintheformofworsenednauseaand vomitingthanprovideimprovedpaincontrol.[26]

  Dixitetal.2022reportedthatsurgeryasariskfactorforopioiduse, persistence,andmisuseinchildren.Intheexperiment,849(63.1%)of1344 pediatricambulatorysurgerypatients responded. Surveyrespondentswere60% male,55%2–12-year-olds,and90%ASA1or2patients.Theaverage proceduretook1h.32.4%of275dischargedpatientsreceivedopioids.164 (59.6%)postoperativeopioidusersdidnotusethemonPOD1.Orthopedicandplasticsurg

eryhad28–29%wastedopioidprescribing,whiledentistryand ophthalmologyhad3–4%.Neurosurgicalpatientsreceived55%opioidsandall usedthemonPOD1.Obstetrics,dentalandmaxillofacialsurgery,orthopedic surgery,andplasticsurgerydischargedatleast60%ofpatientsonopioids,with 33–42%notusingopioidsonPOD1.Operativeandpatient-specificopioiddays andOMEsperkilogramdifferedsubstantially.Somechildrenhad3-to7-day opioidprescriptionsaftertonsillectomyandadenoidectomy,whileonereceived >15 days.Some patients received opioids for10daysafterorchiopexy. Mostgot 2–4days.Thesefindingsrepresentoralmorphineequivalentsperkilogram. Olderpatients,thosewithprivateinsurance,thosewithlongersurgeries,and thosefurthestfromthehospitalwereprescribedmoreopioids.Medicalopioid exposuremakesadolescentsmorelikelytouserecreationally,share,and developdrugdependenceandmisuse.Opioidexposureandchronicusageare linkedtosurgery,with6-10%ofopioid-naïvepersonsconsumingopioidsfor beyond3monthsorevenayearaftersurgery.Aftercholecystectomy, arthroscopickneesurgery,colectomy,andwisdomtoothextraction,5%of pediatricpatientsfillopioidprescriptions2–6monthslater.[27]

Otheropioid-relatedissues,suchasopioidusedisorder,stemfrom opioidusage.In2016,thereareabout153,000childrenin12–17-year-oldsin theUSreportedopioidusedisorder.Mostopioidusedisordercases(99%) involvedprescriptionopioids,withheroinaccountingfor1%.Opioidsarethe leadingcauseofseriousinjuryordeathinchildren,andaccidentalopioid overdosesintheUSdoubledfrom1999to2008.In2008,opioid-related accidentaldeathswere0.1per100,000forchildren0–14and3.7per100,000 forteenagers15–18.After2008,opioid-relatedadolescentmortalitydroppedto 2.0 per 100,000in2011and 2.5per100,000in2015.[28–30]

4.CONCLUSION

Thisbriefreviewshowedthatallresearcherandclinicianagreedthatpost operativeanalgesiamanagementforchildrenstillmustbestartedbyusing acetaminophenasinitialteraphy,then NSAIDandOpioidsasthelastchoice.

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